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EFFICACY AND COMPLICATIONS OF ESOPHAGEAL STENTING FOR ANASTOMOTIC FISTULAS AFTER OPERATED ESOPHAGEAL AND GASTRIC NEOPLASM

ABSTRACT OF THE DOCTORAL THESIS

PhD supervisor:

Prof. Dr. Constantinoiu Silviu

Student-doctorand:

Rosianu Gelu-Cristian

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LIST OF PUBLISHED SCIENTIFIC PAPERS

1. RISK FACTORS OF ANASTOMOTIC FISTULAS AFTER ESOPHAGEAL AND GASTRIC CANCER SURGERY: A RETROSPECTIVE STUDY, C. G. Rosianu, P. Hoara, Rodica Birla,
A. Constantin, D. Predescu, F. Achim, S. Constantinoiu, – Rev. Med. Chir. Soc. Med. Nat., Iaşi 2025, 129(1): 5-189, 10.22551/MSJ.2025.01.16 (Pagina 93)
2. EFFICIENCY AND COMPLICATIONS OF ESOPHAGEAL STENTING IN THE MANAGEMENT OF POSTOPERATIVE FISTULAS, Cristian Gelu Rosianu, Andreea Puscasu, Petre Hoara, Dragos Predescu, Rodica Birla, Florin Achim, Vlad Codrut Strimbu, Silviu Constantinoiu, Octavian Andronic, Alexandru Constantinescu, J. Clin. Med. 2024, 13, 6167, 10.3390/jcm13206167. (Pagina 113)
3. THE USE OF ESOPHAGEAL STENTS IN THE MANAGEMENT OF POSTOPERATIVE FISTULAS—CURRENT STATUS CLINICAL OUTCOMES AND PERSPECTIVES—REVIEW, Rosianu, C.G.; Hoara, P.; Achim, F.; Birla, R.; Bolocan, A.; Mohssen, A.; Copca, N.; Constantinoiu, S., Life 2023, 13, 966. 10.3390/life13040966 (Pgina 40)
4. THE ROLE OF ESOPHAGEAL STENTING IN THE MANAGEMENT OF ANASTOMOTIC LEAKS AFTER ESOPHAGEAL AND ESOPHAGO-GASTRIC CANCER RESECTIONS.
LITERATURE REVIEW, Cristian Gelu Rosianu, Petre Hoara, Alkadour Abdullah, Florin Achim, Rodica Birla, Silviu Constantinoiu, Chirurgia (2022) 117: 175-179, 10.21614/chirurgia.2711 (Page 47)

INTRODUCTION

Anastomotic fistulas are one of the most serious postoperative complications that can occur after surgery for esophageal and gastric neoplasms. They are associated with significant morbidity, prolonged hospitalization, increased medical costs and, in some cases, considerable mortality. Effective management of anastomotic fistulas thus represents a major challenge in surgical practice and requires a multidisciplinary approach to improve clinical outcomes.

An innovative method that has gained more and more popularity in recent years is the use of esophageal stents. These devices, originally developed for the management of esophageal strictures and obstructions, have been adapted to cover and treat anastomotic fistulas, reducing leakage and promoting healing. However, the effectiveness of this method is not universally accepted, and its use remains a matter of debate, especially because of the potential complications associated with it. Studying the efficacy and complications of esophageal stenting in the context of postoperative anastomotic fistulas is crucial to better define the indications for this procedure and to establish evidence-based therapeutic protocols. Understanding the factors that influence the success of this method can also help reduce complications and optimize patient outcomes.

This doctoral thesis aims to analyze in depth the theoretical and practical aspects related to esophageal stenting, focusing on the efficiency of the method and the associated complications. Through a systematic approach to the literature and through the analysis of clinical data, we aim to provide a complete and up-to-date guide for clinicians managing this category of patients.

THEORETICAL CONSIDERATIONS

Anastomotic fistulas are one of the most severe postoperative complications that can occur after surgery for esophageal and gastric neoplasms. They consist of an abnormal communication between the lumen of the digestive tract and the surrounding structures or the external environment, as a result of partial or total dehiscence at the level of the anastomosis line. This complication has a significant impact on morbidity, prolonging hospitalization and increasing mortality, being associated with delayed healing, severe infections, and deterioration of digestive tract functionality (81).

Anastomotic fistulas result from a complex combination of local, systemic and technical factors, each contributing differently to compromising the healing process at the level of the anastomosis. Understanding these mechanisms is essential to prevent this severe complication and optimize postoperative outcomes (123).

A major local factor in the appearance of fistulas is tissue ischemia at the level of the anastomosis, caused by inadequate vascularization of the segments involved in surgical reconstruction. Reduced blood flow compromises the supply of oxygen and nutrients necessary for the cell regeneration process and the formation of granulation tissue, essential for healing. This situation is common in gastric tube transposition or other esophageal substitutions, where excessive length or tension can affect the vascularization of the distalized segments (124–126).

The incidence of anastomotic fistulas varies significantly depending on the type of surgery, the location of the anastomosis, and the clinical characteristics of the patient. These variations reflect differences in the techniques used, in the complexity of interventions and in the associated risk factors (107,135).

Esophageal stenting is a minimally invasive therapeutic method, frequently used in the management of anastomotic fistulas. It has evolved significantly over time, becoming one of the main options for reducing complications associated with fistulas and promoting healing. The use of esophageal stents has been influenced by technological innovations and a better understanding of the pathological mechanisms involved in anastomotic fistulas (178).

The first attempts to use stents for the management of esophageal problems date back to the second half of the twentieth century. Initially, rigid stents made of materials such as plastic

or stainless steel have been used to treat benign or malignant esophageal strictures. These devices had significant drawbacks such as patient discomfort, excessive stiffness, and increased risk of perforation (179).

Modern implantation devices allow precise positioning of stents, even in difficult anatomical areas. This significantly reduced complications related to incorrect placement or migration of stents.

The development of customized stents, tailored to the size and shape of individual fistulas, improved treatment efficiency. These devices are manufactured based on preoperative imaging and provide optimal adaptation to the patient's anatomy (178).

PURPOSE AND OBJECTIVES

Purpose of the study

The purpose of this study is to evaluate the efficacy and complications of esophageal stenting as a therapeutic method for the treatment of postoperative anastomotic fistulas in patients operated for esophageal and gastric neoplasms.

Specific objectives

1. The objective of this study is to identify the demographic, clinical and surgical characteristics of patients operated for esophageal and gastric neoplasms.
2. Determination of the incidence of postoperative anastomotic fistulas and analysis of their characteristics (location, size, severity) among patients in the study group.
3. Investigation of clinical, surgical, and postoperative risk factors associated with the occurrence of anastomotic fistulas, using statistical methods to assess significant relationships.
4. Evaluation of the efficiency of endoscopic stenting in the closure of anastomotic fistulas
5. Analysis of the type, frequency and severity of post-stent complications (e.g., stent migration, perforations, obstructions) and their impact on clinical evolution.

STUDY METHODOLOGY

Research Design

This **retrospective** and **observational** study was conducted to evaluate the efficacy and complications of esophageal stenting in the treatment of postoperative anastomotic fistulas in patients operated for esophageal and gastric neoplasms, compared to a control group. The analysis was carried out based on data from patients admitted to the Surgery Clinic of St. Mary's Hospital in Bucharest, between 2019 and 2023. The data was collected and processed between 2023 and 2024.

The study population was divided into two groups:

Study Group: Patients who developed postoperative anastomotic fistulas and were treated with endoscopic esophageal stenting

Control group: Patients operated for esophageal and gastric neoplasms, but who did not develop postoperative fistulas.

The eligibility criteria were:

- Patients at least 18 years of age.
- Diagnosis of histopathologically confirmed esophageal or gastric neoplasm
- Presence of image-confirmed anastomotic fistulas for the study group
- Patients without anstomotic fistulas for the control group.
- Patients with insufficient medical data were excluded

The data required for this retrospective and observational study were collected using medical records, clinical observation records and electronic databases. For the centralization and efficient organization of the information, the Microsoft Excel application was used.

Patients were selected according to eligibility criteria, and each case was checked for completeness of data. Each case was entered in tabular form,and the clinical and demographic variables were organized into relevant categories, as follows:

Demographics: age, gender.

Clinical parameters: diagnosis, TNM staging, comorbidities.

Information about fistulas: location, size and time of their appearance.

Interventions and results: type of stent used, its duration, complications, length of hospitalization and status at discharge.

The data was checked in two stages to ensure consistency and accuracy:

- Initial check, to eliminate possible input errors.
- Validation through comparison with Documents original for a representative sample.

The research was carried out in accordance with all ethical norms on scientific research, applicable both nationally and internationally, to ensure the integrity of the research process and the protection of patients.

The study complied with the regulations provided by Law 206/2004 on good conduct in scientific research, technological development and innovation, which establishes ethical and integrity standards in the research activity carried out in Romania. In addition, the recommendations of the Declaration of Helsinki, which represent an essential international framework for the ethics of medical research on human subjects, have been implemented. The fundamental principles of this statement, such as protecting privacy and respecting patients' rights, were respected throughout the study.

The study was retrospective and descriptive, using only existing clinical data, without influencing in any way the therapeutic management of patients.

The research did not involve direct contact with patients or changes to the treatment plan applied in clinical practice.

All data collected has been anonymized to protect the identity and privacy of patients. The anonymization systems have been implemented in accordance with the GDPR (General Data Protection Regulation) regulations.

In order to protect patient data, it has been processed exclusively in an anonymised format. Each case was identified by a unique code, removing any personally identifiable information. This method ensured compliance with current European data protection legislation (GDPR).

RESULTS

Of the total of 110 cases analyzed, 68 are male, representing 61.82% of the study group, and 42 are female, corresponding to a percentage of 38.18%.

Of the total of 110 patients included in the study, the mean age is 56.92 years, and the median is 55 years, with a standard deviation of 8.31 years, indicating a moderate variation in age in the study group. The minimum registered age is 41 years old, and the maximum is 80 years old. The graph in figure no. 3 highlights an asymmetrical distribution of patients' age, with a peak around the age of 55-60 years. Most patients are concentrated between 50 and 60 years old, while cases in the extreme age categories (40-50 years old and over 70 years old) are less frequent.

The distribution of patients according to the location of the tumor formation shows that the majority of cases are located in the mid-body gastric region, accounting for 34.55% (38 cases), followed by subcardial formations (Siewert III) with 26.36% (29 cases). Tumors located at the level of the lower esophagus (Siewert I) were registered in 18.18% of the patients (20 cases), and those located at the level of the esogastric junction (Siewert II) in 11.82% (13 cases). Formations in the middle esophagus were the least common, being present in 9.09% of patients (10 cases).

The endoscopic size of tumor formations in patients included in the study ranges from 2,000 cm to 4,000 cm, with a mean of 2,950 cm and a median of 3,000 cm. The standard deviation of 0.613 cm indicates a small variation in tumor size in the studied group (Table no. and Figure no.). The distribution of the endoscopic size of the tumor formations shows that most of the cases (68 patients, 61.82%) have formations with a size of 3 cm. Tumors of 2 cm were registered in 23 patients (20.91%), while tumors of 4 cm are present in 18 patients (16.36%). Formations of 2.5 cm were rare, being found in a single patient (0.91%). Dimensions smaller than 3 cm predominate in the studied group, accumulating 83.64% of the cases.

Of the total of 110 patients included in the study, 44 (40.00%) received preoperative radiotherapy, while 66 (60.00%) did not undergo this type of treatment before surgery (Table no. XXII and Figure no. 26)

The most commonly used surgery was total gastrectomy with terminolateral esojejunoanastomosis, performed in 74 patients (67.27%). The Ivor Lewis procedure was performed in 30 patients (27.27%), while McKeown esogastrectomy was used in 5 cases (4.55%). Subtotal esogastrectomy with end-to-end esogastric anastomosis was rare, being performed in a single patient (0.91%). Of the 110 patients, 106 (96.36%) benefited from curative interventions, while 4 patients (3.64%) underwent palliative interventions.

Of the 110 patients included in the study, 55 (50.00%) developed anastomotic fistulas, while the other 55 (50.00%) did not have this complication. The distribution is equal between the two categories, according to the study methodology. Of the 55 cases with anastomotic fistulas, 34 (61.82%) were located at the level of the eso-jejunal anastomosis, and 21 (38.18%) at the level of the eso-gastric anastomosis. The main method of diagnosis of anastomotic fistula was full body CT scan with contrast agent administered intravenously and orally, used in 47 cases (85.45%). Eso-jejunal transit with ionic contrast agent was used in 8 cases (14.55%).

Of the 55 cases with anastomotic fistulae, the time of their appearance varies between 5 and 10 days postoperatively, with an average of 7.44 days and a median of 7 days. The standard deviation of 1.29 days indicates reduced variability between patients (Table no. XXXXII and Figure no. 36 and 37). The graph in figure no. XX shows the distribution of cases according to the number of days until the appearance of the postoperative anastomotic fistula. Most cases (15) are concentrated on the 7th postoperative day, followed by the 8th day with a close number of cases. The number of cases gradually decreases for days 5, 6 and 10, emphasizing the fact that the 7-8 days interval represents the most critical moment for the occurrence of this complication.

Of the 110 patients included in the study, 7 (6.36%) developed esopleural fistulae, while 103 (93.64%) did not experience this complication. 15 patients (13.64%) were diagnosed with mediastinitis or mediastinal abscess, while 95 (86.36%) did not have these complications. Of the 15 cases in which mediastinitis or peritonitis was diagnosed, the germs most frequently involved were Escherichia coli (6 cases, 40.00%) and Klebsiella (5 cases, 33.33%). Co-infections were present in 4 cases (26.67%), of which the combination of Escherichia coli and Klebsiella was found in 2 cases (13.33%), and the combinations of Escherichia coli and Pseudomonas aeruginosa and Klebsiella and Pseudomonas aeruginosa were found in 1 case (6.67% each).

Of the total of 110 patients included in the study, 105 (95.45%) survived postoperatively and were discharged in stable condition, while 5 patients (4.55%) died in the postoperative period. Of the 5 postoperative deaths, the main causes were: sepsis with mediastinitis, reported in 3 cases (2.73%), followed by eso-tracheal fistula and post-endoscopic stenting aorto-esophageal fistula, each recorded in a single case (0.91%).

In the majority of cases (92.73%), a single stent was used for the management of anastomotic fistulas. In only 7.27% of cases, two stents were required (one Cardia Umbrella 28/140 mm Total Coated and 3 Total Coated 24/100 mm). The most common type of stent initially used was fully covered 24/100 mm, applied in 54.55% of cases, followed by Cardia Umbrella 36/140 mm fully covered, used in 30.91% of cases. Other types of stents, such as total covered 24/120 mm and total covered 22/100 mm, were used less frequently, together accounting for 12.73% of cases.

Of the 55 patients who underwent endoscopic stenting for the management of anastomotic fistulas, the method proved effective in most cases. The fistula was completely closed after the use of a single stent in 89.09% of cases (49 patients), and a second stent was required to achieve closure in 7.27% of cases (4 patients). In only 3.64% of cases (2 patients), the fistula remained open even after the stent procedure.

After stent removal, 96.36% of patients (53 cases) had completely healed anastomoses, with only 3.64% of patients (2 cases) having persistent fistulas. These data highlight a high success rate of endoscopic stenting in the treatment of postoperative anastomotic fistulas, emphasizing the effectiveness of the method in most cases.

However, cases that require a second stent or in which the fistula persists after stent extraction indicate the presence of complicated factors, such as ischemia, tension on the anastomosis, or the initial large size of the fistula, which can affect the healing process. These results confirm the usefulness of stenting as a first-line method, but also emphasize the need for close monitoring and additional interventions for patients with an incomplete response to treatment.

Of the 55 patients who benefited from endoscopic stenting, 12 (21.82%) had complications, while 43 (78.18%) reported no post-procedural problems. The most common complications included upper gastrointestinal hemorrhage at the proximal end of the stent (7.27%), perforation peritonitis at the distal end of the stent (3.64%), and stent migration to

the level of the jejunal loop (3.64%). Other rare complications, such as eso-tracheal fistula or distal digestive haemorrhage, were reported in one case each (1.82%).

The management of these complications involved advanced endoscopic techniques, such as fitting clips through the scope (7.27%) and stent extraction followed by fitting a new clip-fixed stent (7.27%). Surgical procedures, such as drainage and peritoneal lavage, were required in 3.64% of cases, and the fitting of OTSC clips was applied in only one case (1.82%).

Complications occurred in a range ranging from 6 to 42 days post-stenting, with the majority reported within the first 32 days. This early post-procedural period is considered critical, requiring close monitoring for the detection and prompt treatment of possible complications.

The results indicate that endoscopic stenting is an effective method, but associated with moderate risks of complications. The choice of appropriate stents, the application of prophylactic techniques and intensive post-procedural monitoring are essential to reduce these risks and optimize clinical outcomes.

Of the 55 patients who underwent endoscopic stenting to close the anastomotic fistula, the stent maintenance period ranged from 14 to 42 days, with an average of 32.82 days and a median of 33 days. The standard deviation of 4.85 days indicates a moderate variation, concentrated around the median. Analysis of the distribution graph shows a concentration of cases in the range of 30-35 days, which suggests a standardized practice for most patients. However, there are also a few isolated cases with shorter (less than 20 days) or longer (close to 42 days) periods.

DISCUSSIONS

The age distribution of the patients in this study, with an average of about 57 years, is consistent with data from the literature that emphasizes that esophageal and gastric neoplasms are more common in people in the sixth decade of life. Similar studies have reported an increased incidence of these types of neoplasms in patients aged 50–70 years (208,219–221).

Almost half of the patients (46.36%) have at least one comorbidity, which reflects the complexity of the cases included in the study. The prevalence of hypertension (32.73%) is

in line with data from the literature, which highlight hypertension as one of the most common comorbidities associated with patients with esophageal and gastric neoplasms. The prevalence of diabetes mellitus (14.55%) is slightly lower, but remains within the limits reported by similar studies, which indicate diabetes as an additional risk factor for the unfavorable evolution of these patients. These comorbidities influence both the prognosis and therapeutic management of patients, contributing to an increased risk of postoperative complications and affecting overall recovery (46,51,230).

The observed distribution reflects the predominance of tumors located in the gastric and subcardial region, which is consistent with the literature, which indicates a higher incidence of gastric neoplasms compared to esophageal ones. Tumor formations located in the Siewert II and III zones are recognized as critical points, as they imply increased complexity in surgical management and potentially lower survival due to the strategic location at the eso-gastric junction.

The presence of anastomotic fistulas reflects a major and frequent complication in gastroesophageal surgery, which is associated with a significant impact on the postoperative evolution. The predominant location at the level of the esojejunal anastomosis (61.82%) is consistent with the literature, which indicates a higher incidence of fistulas in this segment due to the technical complexity and local vascularization. Esogastric fistulas (38.18%) are less common, but remain an important cause of morbidity.

The predominant imaging diagnosis by full body CT scan with contrast, used in 85.45% of cases, highlights this method as the gold standard for detecting fistulas, due to its high sensitivity and specificity.

The appearance of fistulas on average at 7.44 days postoperatively is consistent with the literature, which indicates this period as the critical interval for the detection of anastomotic fistulas, especially due to the inflammatory and healing processes that occur at this stage. The median of 7 days suggests a predictable time for the manifestation of the complication, and the reduced variability reflected by the standard deviation emphasizes the consistency of this interval. The concentration of cases in the 7-8 days interval is consistent with the literature, which emphasizes that postoperative inflammation and mechanical stresses reach critical values during this period, increasing the risk of anastomotic dehiscence (161,218).

These data underline the importance of intensive surveillance in the first postoperative week, the period when the risk of fistulization is highest. Standardization of clinical and imaging controls during this interval can contribute to the early detection and reduction of morbidity associated with anastomotic fistulas.

These data highlight the need for a personalized approach in the management of elderly patients, including optimized surgical techniques, close monitoring and prophylactic interventions to reduce the risk of anastomotic fistulae.

The results indicate a significant association between preoperative radiotherapy and the increased risk of anastomotic fistulas. Radiotherapy can affect local vascularization and tissue quality, increasing susceptibility to dehiscence and other postoperative complications. Data from published studies confirm this adverse effect, especially in cases with advanced tumors, where high doses of radiation can compromise the healing process of the anastomosis. Although preoperative chemotherapy does not appear to be associated with an increased risk of anastomotic fistulas, the difference observed between groups is not statistically significant. This suggests that the effects of chemotherapy on fistula risk are less pronounced compared to radiotherapy (207).

Endoscopic stenting is a modern and effective method in the management of anastomotic fistulae, offering a minimally invasive alternative to classic surgeries. This technique allows the isolation of the affected area, reduces external leakage and facilitates the healing process, without the need for major surgery. In addition, endoscopic stenting contributes to reducing stress on the patient, limiting the complications associated with a new intervention and improving the quality of life in the postoperative period. This benefit is supported by the high rates of fistula closure observed in recent studies, including data from the present study (203,210).

Another important aspect of using endoscopic stenting is its flexibility in managing complex complications. The choice of stent type and duration of maintenance can be adapted to the individual characteristics of the patient, including the size and location of the fistula. Also, modern technology allows the application of coated stents, which provide additional protection against migration and perforation, contributing to an increased success rate. In situations where initial stenting is not sufficient, the use of a second stent or adjuvant techniques such as endoscopic clips may optimize clinical outcomes (200).

The use of endoscopic stenting also has a significant impact on medical resources and associated costs. By reducing the need for additional surgery and shortening the length of hospital stay for most patients, this technique offers a cost-effective solution for the management of anastomotic fistulae. However, proper patient selection and rigorous post-procedure monitoring are important to minimize the risk of complications, such as stent migration or hemorrhages, which can prolong hospitalization and require additional interventions. These benefits underscore the value of endoscopic stenting as an essential component in the modern therapeutic arsenal of gastroesophageal surgery (179).

These results support the use of endoscopic stenting as a first-line method in the management of anastomotic fistulas, but also emphasize the importance of strict post-extraction monitoring for the early identification of resistant cases. Additional strategies, such as nutritional therapy and local support, could improve outcomes in complex cases.

CONCLUSIONS

1. Anastomotic fistulas were more common in patients with larger tumors and mid-body or subcardial gastric localization (Siewert III), suggesting that tumor size and location influence the risk of complications.
2. Tumor stage advancement (T3-T4 and N2) has been associated with a significant increase in the risk of fistulas, highlighting the importance of early diagnosis and treatment of gastroesophageal neoplasms.
3. Endoscopic stenting proved to be effective in 96.36% of cases, with complete closure of the fistula after stent extraction, which confirms the usefulness of this method in the management of anastomotic fistulas.
4. Approximately 21.82% of stented patients had complications, the most common being hemorrhages and stent migration. These results underline the need for strict monitoring and appropriate device selection.
5. The average stent maintenance period was approximately 33 days, suggesting that this duration is sufficient for most fistulas to heal, but should be adjusted according to the patient's individual response.

RESEARCH CONTRIBUTIONS

This research makes significant contributions to the understanding and management of postoperative anastomotic fistulas in patients with esophageal and gastric neoplasms, having important implications both for clinical practice and for the optimization of therapeutic strategies.

The study highlighted a clear set of risk factors for the occurrence of anastomotic fistulas, such as advanced age, the presence of comorbidities (hypertension, diabetes), altered biological parameters (low serum albumin, low hemoglobin, increased creatinine, hyperglycemia) and tumor stage advancement (T3-T4 and N2). This information contributes to better patient selection and preparation before surgery, reducing the risk of postoperative complications.

Research demonstrates that endoscopic stenting is a safe and effective method, with a 96.36% success rate in closing anastomotic fistulae. This finding underscores the usefulness of stenting as a first-line treatment for such complications, offering a minimally invasive and less traumatic alternative to resurgeries.

The study documented complications associated with stenting, including hemorrhages, stent migration, and perforations, and identified effective therapeutic solutions, such as the use of endoscopic clips, peritoneal drainage, and additional stenting. This information provides practical guidance for managing complex situations, helping to improve clinical outcomes.

SELECTED BIBLIOGRAPHY

7. Yazaki E, Sifrim D. Anatomy and physiology of the esophageal body. Diseases of the Esophagus. 2011 Mar 8; 25(4):292–8.
8. EŞREFOGLU M, TASLIDERE E, CETIN A. Development of the Esophagus and Stomach. Bezmialem Science. 2018 Feb 22; 175–82.
9. Su A, Parker CH, Conklin JL. Esophageal anatomy and physiology. In: Clinical and Basic Neurogastroenterology and Motility [Internet]. Elsevier; 2020. p. 79–88. Available from: http://dx.doi.org/10.1016/b978-0-12-813037-7.00005-4
10. Bandyopadhyay N, Fass R, Yamasaki T, Hemond C. Introduction. In: Pocket Handbook of Esophageal Disorders [Internet]. Springer International Publishing; 2018. p. 1–1. Available from: http://dx.doi.org/10.1007/978-3-319-97331-9_1
11. Blanchard SS, Czinn SJ. Developmental Anatomy and Physiology of the Stomach. In: Pediatric Gastrointestinal and Liver Disease [Internet]. Elsevier; 2021. p. 246-252.e1. Available from: http://dx.doi.org/10.1016/b978-0-323-67293-1.00024-4

12. Hunt RH, Camilleri M, Crowe SE, El-Omar EM, Fox JG, Kuipers EJ, et al. The stomach in health and disease. Gut. 2015 Sep 4; 64(10):1650–68.
32. Ramsay PT, Carr A. Gastric Acid and Digestive Physiology. Surgical Clinics of North America. 2011 Oct; 91(5):977–82.
33. Chu S, Schubert ML. Gastric secretion: Current Opinion in Gastroenterology. 2013 Nov; 29(6):636–41.
34. Schubert ML. Gastric acid secretion. Current Opinion in Gastroenterology. 2016 Nov; 32(6):452–60.
35. Schubert ML. Functional anatomy and physiology of gastric secretion: Current Opinion in Gastroenterology. 2015 Nov; 31(6):479–85.
36. McBride PJ, Hinder RA, Raiser F, Katada N. Lower esophageal sphincter as an anti-reflux barrier: a review. Diseases of the Esophagus. 1997 Apr 1; 10(2):101–4.
37. Dunn CP, Wu J, Gallagher SP, Putnam LR, Bildzukewicz NA, Lipham JC. Understanding the GERD Barrier. Journal of Clinical Gastroenterology. 2021 Jul; 55(6):459–68.
38. Holloway RH. The anti-reflux barrier and mechanisms of gastro-oesophageal reflux. Best Practice & Research Clinical Gastroenterology. 2000 Oct; 14(5):681–99.
39. Mussa BM, Sood S, Verberne AJ. Implication of neurohormonal-coupled mechanisms of gastric emptying and pancreatic secretory function in diabetic gastroparesis. WJG. 2018 Sep 14; 24(34):3821–33.
40. Sharkey KA, Mawe GM. Neurohormonal signalling in the gastrointestinal tract: new frontiers. J Physiol. 2014 Jul 15; 592(14):2923–5.
54. Venerito M, Vasapolli R, Rokkas T, Malfertheiner P. Gastric cancer: epidemiology, prevention, and therapy. Helicobacter [Internet]. 2018 Sep; 23(S1). Available from: http://dx.doi.org/10.1111/hel.12518
55. A. B, B. K, S. AD, M. AK, J. R, R. H, et al. Surgical treatment of esophageal cancer in the era of multimodality ma nagement. Annals of the New York Academy of Sciences [Internet]. 2018; Available from: https://nyaspubs.onlinelibrary.wiley.com/doi/pdfdirect/10.1111/nyas.13677
56. A. P, Jie Z, Haiquan C, J. L. The ‘best operation’ for esophageal cancer? Annals of Thoracic Surgery [Internet]. 2010; Available from: https://europepmc.org/articles/pmc3769958?pdf=render
57. Abbas G, Krasna M. Overview of esophageal cancer. Ann Cardiothorac Surg. 2017 Mar; 6(2):131–6.
58. C. MSS, J. L, R. L, Ghulam A. Esophageal cancer: an update. International Journal of Surgery. 2010;
59. H. K, M. F, T. M, M. N, N. T, Takanori I, et al. Surgical Treatment for Esophageal Cancer. Digestive Surgery [Internet]. 2007; Available from: https://www.karger.com/Article/Pdf/101894
60. R. V, D. M. Surgical management of esophageal cancer. Chinese Clinical Oncology. 2017;
61. Boshier PR, Anderson O, Hanna GB. Transthoracic Versus Transhiatal Esophagectomy for the Treatment of Esophagogastric Cancer: A Meta-Analysis. Annals of Surgery. 2011 Dec; 254(6):894–906.
62. Allen MS. Ivor Lewis esophagectomy. Semin Thorac Cardiovasc Surg. 1992 Oct; 4(4):320–3.
63. White A, Kucukak S, Lee DN, Mazzola E, Zhang Y, Swanson SJ. Ivor Lewis minimally invasive esophagectomy for esophageal cancer: An excellent operation that improves with experience. The Journal of Thoracic and Cardiovascular Surgery. 2019 Feb; 157(2):783–9.

64. Marsh AM, Buicko Lopez JL. Gastric Resection for Malignancy. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Dec 19]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK560760/
65. Kitamura K, Yamaguchi T, Nishida S, Yamamoto K, Ichikawa D, Okamoto K, et al. The operative indications for proximal gastrectomy in patients with gastric cancer in the upper third of the stomach. Surg Today. 1997 Nov; 27(11):993–8.
66. Kolozsi P, Varga Z, Toth D. Indications and technical aspects of proximal gastrectomy. Front Surg. 2023 Feb 16;10:1115139.
67. Lin HW, Loh EW, Shen SC, Tam KW. Gastrectomy with or without omentectomy for gastric cancer: A systematic review and meta-analysis. Surgery. 2022 May; 171(5):1281–9.
68. Liu Z, Feng F, Guo M, Liu S, Zheng G, Xu G, et al. Distal gastrectomy versus total gastrectomy for distal gastric cancer. Medicine (Baltimore). 2017 Feb; 96(5):e6003.
69. Kolozsi P, Varga Z, Toth D. Indications and technical aspects of proximal gastrectomy. Front Surg. 2023 Feb 16;10:1115139.
70. Lou S, Yin X, Wang Y, Zhang Y, Xue Y. Laparoscopic versus open gastrectomy for gastric cancer: A systematic review and meta-analysis of randomized controlled trials. International Journal of Surgery. 2022 Jun;102:106678.
71. Markar SR, Visser M, Van Der Veen A, Luyer M, Nieuwenhuijzen GA, Stoot JH, et al. Evolution in Laparoscopic Gastrectomy from a Randomized Controlled Trial through National Clinical Practice. Annals of Surgery [Internet]. 2023 Nov 23 [cited 2024 Dec 19]; Available from: https://journals.lww.com/10.1097/SLA.0000000000006162
72. Yamamoto K, Omori T, Kurokawa Y, Takeno A, Akamaru Y, Demura K, et al. Laparoscopic Gastrectomy for Advanced Gastric Cancer. The American SurgeonTM. 2023 Dec; 89(12):5660–8.
73. Ke B, Liang H. Current status of lymph node dissection in gastric cancer. Chinese Journal of Cancer Research. 2021; 33(2):193–202.
74. Naffouje SA, Salti GI. Extensive Lymph Node Dissection Improves Survival among American Patie nts with Gastric Adenocarcinoma Treated Surgically: Analysis of the Na tional Cancer Database. J Gastric Cancer. 2017; 17(4):319.
75. Batista TP, Martins MR. Lymph node dissection for gastric cancer: a critical review. Oncol Rev. 2012 Jun 25; 6(1):12.
76. Tamura S, Takeno A, Miki H. Lymph Node Dissection in Curative Gastrectomy for Advanced Gastric Can cer. International Journal of Surgical Oncology. 2011; 2011:1–8.
77. de Steur WO, Dikken JL, Hartgrink HH. Lymph Node Dissection in Resectable Advanced Gastric Cancer. Dig Surg. 2013; 30(2):96–103.
78. Tanizawa Y, Terashima M. Lymph node dissection in the resection of gastric cancer: Review of ex isting evidence. Gastric Cancer. 2010 Aug; 13(3):137–48.
79. Nico R, Veziant J, Chau A, Eveno C, Piessen G. Optimal lymph node dissection for gastric cancer: a narrative review. World J Surg Onc [Internet]. 2024 Apr 23; 22(1). Available from: http://dx.doi.org/10.1186/s12957-024-03388-4
80. Wu W, Dong P, Wu X, Li M, Ding Q, Zhang L, et al. Three-step method for systematic lymphadenectomy in gastric cancer sur gery using the ‘curettage and aspiration dissection technique’ with Pe ng’s multifunctional operative dissector. World J Surg Onc [Internet]. 2014 Oct 24; 12(1). Available from: http://dx.doi.org/10.1186/1477-7819-12-322

81. Barchi LC, Ramos MFKP, Pereira MA, Dias AR, Ribeiro-Júnior U, Zilberstein B, et al. Esophagojejunal anastomotic fistula: a major issue after radical total gastrectomy. Updates Surg. 2019 Sep; 71(3):429–38.
Jun; 7:10–10.
93. Sánchez-Pernaute A, Pérez-Aguirre E. Gastroesophageal reflux after Roux-en-Y gastric bypass: Is it just related to technical details? Cirugía Española (English Edition). 2023 Oct; 101:S58–62.
94. Moorcraft SY, Smyth EC, Cunningham D. Adjuvant or neoadjuvant therapy for operable esophagogastric cancer? Gastric Cancer. 2014 Mar 18; 18(1):1–10.
95. D. P, R. P, P. G. Neoadjuvant Therapy and Lymphadenectomy in Esophageal Cancer: Both Are Essential to Maximize Survival Benefit. Annals of Surgery. 2015;
96. Schirren R, Reim D, Novotny AR. Adjuvant and/or neoadjuvant therapy for gastric cancer? A perspective review. Ther Adv Med Oncol. 2014 Nov 17; 7(1):39–48.
97. Fujitani K. Overview of Adjuvant and Neoadjuvant Therapy for Resectable Gastric Ca ncer in the East. Dig Surg. 2013; 30(2):119–29.
98. Lee Y, Samarasinghe Y, Lee MH, Thiru L, Shargall Y, Finley C, et al. Role of Adjuvant Therapy in Esophageal Cancer Patients After Neoadjuva nt Therapy and Esophagectomy. Annals of Surgery. 2021 Sep 29; 275(1):91–8.
99. Xiao X, Hong HG, Zeng X, Yang YS, Luan SY, Li Y, et al. The Efficacy of Neoadjuvant versus Adjuvant Therapy for Resectable Eso phageal Cancer Patients: Direct and Indirect Comparisons *via* Meta-Analysis. SSRN Journal [Internet]. 2019; Available from: http://dx.doi.org/10.2139/ssrn.3514750
100. Altorki N, Harrison S. What is the role of neoadjuvant chemotherapy, radiation, and adjuvant treatment in resectable esophageal cancer? Ann Cardiothorac Surg. 2017 Mar; 6(2):167– 74.
101. Kamarajah SK, Evans RPT, Nepogodiev D, Hodson J, Bundred JR, Gockel I, et al. The influence of anastomotic techniques on postoperative anastomotic c omplications: Results of the Oesophago-Gastric Anastomosis Audit. The Journal of Thoracic and Cardiovascular Surgery. 2022 Sep; 164(3):674-684.e5.
102. Yuan Y, Wang KN, Chen LQ. Esophageal anastomosis. Dis Esophagus. 2014 Jan 20; 28(2):127–37.
103. Kim RH, Takabe K. Methods of esophagogastric anastomoses following esophagectomy for can cer: A systematic review. Journal of Surgical Oncology. 2010 Apr 9; 101(6):527–33.
104. Herron R, Abbas G. Techniques of Esophageal Anastomoses for Esophagectomy. Surgical Clinics of North America. 2021 Jun; 101(3):511–24.
105. Biere SSAY, Maas KW, Cuesta MA, van der Peet DL. Cervical or Thoracic Anastomosis after Esophagectomy for Cancer: A Sys tematic Review and Meta-Analysis. Dig Surg. 2011; 28(1):29–35.
106. Cerfolio RJ, Allen MS, Deschamps C, Trastek VF, Pairolero PC. Esophageal replacement by colon interposition. The Annals of Thoracic Surgery. 1995 Jun; 59(6):1382–4.
107. Ferrante F, Bassi M, Diso D, Ferreira Vaz Sousa R, Paganini AM, Venuta F, et al. A challenging upper digestive tract continuity restoration after recurrent esophago-colonic anastomosis complications. J Cardiothorac Surg. 2022 Dec 17; 17(1):318.
108. Yang K, Zhang W, Chen Z, Chen X, Liu K, Zhao L, et al. Comparison of long-term quality of life between Billroth-I and Roux-en-Y anastomosis after distal gastrectomy for gastric cancer:

a randomized controlled trial. Chinese Medical Journal [Internet]. 2023 Apr 5 [cited 2024 Dec 19]; Available from: https://journals.lww.com/10.1097/CM9.0000000000002602
109. Shahbazyan SS, Sahakyan MA, Gabrielyan A, Lai X, Martirosyan A, Petrosyan H, et al. Billroth-I anastomosis in distal subtotal gastrectomy for non-early gastric adenocarcinoma. Radiology and Oncology. 2023 Sep 1; 57(3):356–63.
123. U. J, K. V, V. M, S. T, E. B. 225. PREDICTORS OF ANASTOMOTIC LEAK AMONG PATIENTS UNDERGOING ESOPHAGE CTOMY: A RETROSPECTIVE COHORT OF 6669 PATIENTS. Diseases of the esophagus [Internet]. 2023; Available from: https://academic.oup.com/dote/article-pdf/36/Supplement_2/doad052.077/51297968/doad052.077.pdf
124. C. AB, A. A, T. J, H. H. Anastomotic leakage after anterior resection for rectal cancer: risk f actors. Colorectal Disease. 2010;
125. Fabbi M, Hagens ERC, van Berge Henegouwen MI, Gisbertz SS. Anastomotic leakage after esophagectomy for esophageal cancer: definit ions, diagnostics, and treatment. Diseases of the Esophagus [Internet]. 2020 Jun 1; Available from: http://dx.doi.org/10.1093/dote/doaa039
126. Ubels S, Verstegen MHP, Rosman C, Reynolds JV. Anastomotic leakage after esophagectomy for esophageal cancer: risk fa ctors and operative treatment. Ann Esophagus. 2021 Mar; 4:8–8.
127. R. O, B. P, Rui S, P. PN, P. B, Joaquim A de S, et al. Anastomotic Leaks following Esophagectomy for Esophageal and Gastroeso phageal Junction Cancer: The Key Is the Multidisciplinary Management. GE: Portuguese Journal of Gastroenterology [Internet]. 2021; Available from: https://www.karger.com/Article/Pdf/520562
128. W. G, Junsheng L. Combat with esophagojejunal anastomotic leakage after total gastrectom y for gastric cancer: A critical review of the literature. International Journal of Surgery. 2017;
135. Hall BR, Flores LE, Parshall ZS, Shostrom VK, Are C, Reames BN. Risk factors for anastomotic leak after esophagectomy for cancer: A NS QIP procedure-targeted analysis. Journal of Surgical Oncology. 2019 Jul 10; 120(4):661–9.
136. Schlottmann F, Molena D. Anastomotic leak: an early complication with potentially long-term con sequences. J Thorac Dis. 2016 Oct; 8(10):E1219–20.
137. Haghdani S, Tabatabai A, Hashemi M, Mohajeri G, Ahmadinejad M, Khan I. Incidence and risk factors predisposing anastomotic leak after transhi atal esophagectomy. Ann Thorac Med. 2009; 4(4):197.
145. Barbaro A, Eldredge TA, Shenfine J. Diagnosing anastomotic leak post-esophagectomy: a systematic review. Diseases of the Esophagus [Internet]. 2020 Aug 10; 34(2). Available from: http://dx.doi.org/10.1093/dote/doaa076
146. E. B, Joshua SH, M. R, J. S, Susie CH, J. S. Drain amylase aids detection of anastomotic leak after esophagectomy. Journal of Gastrointestinal Oncology. 2016;
147. Aiolfi A, Asti E, Rausa E, Bonavina G, Bonitta G, Bonavina L. Use of C-reactive protein for the early prediction of anastomotic leak after esophagectomy: Systematic review and Bayesian meta-analysis. PLoS ONE. 2018 Dec 17; 13(12):e0209272.
163. Turrentine FE, Denlinger CE, Simpson VB, Garwood RA, Guerlain S, Agrawal A, et al. Morbidity, Mortality, Cost, and Survival Estimates of Gastrointestinal Anastomotic Leaks. Journal of the American College of Surgeons. 2015 Feb; 220(2):195–206.
164. PACE M, MINERVINI A, GOGLIA M, CINQUEPALMI M, MOSCHETTA G, ANTOLINO L, et al. Overall Survival Following Anastomotic Leakage After Surgery for Carci

noma of the Esophagus and Gastroesophageal Junction: A Systematic Revi ew. In Vivo. 2023; 37(4):1423–31.
192. Yimcharoen P, Heneghan HM, Tariq N, Brethauer SA, Kroh M, Chand B. Endoscopic stent management of leaks and anastomotic strictures after foregut surgery. Surgery for Obesity and Related Diseases. 2011 Sep; 7(5):628–36.
193. Chang J, Sharma G, Boules M, Brethauer S, Rodriguez J, Kroh MD. Endoscopic stents in the management of anastomotic complications after foregut surgery: new applications and techniques. Surgery for Obesity and Related Diseases. 2016 Aug; 12(7):1373–81.
195. Eisendrath P, Cremer M, Himpens J, Cadière GB, Le Moine O, Devière J. Endotherapy including temporary stenting of fistulas of the upper gast rointestinal tract after laparoscopic bariatric surgery. Endoscopy. 2007 Sep 24; 39(07):625–30.
196. Ladrón Abia P, Mínguez Sabater A, Martínez Delgado S, Alonso N, Argüello L, García Campos M, et al. ESOPHAGEAL STENT PLACEMENT FOR THE TREATMENT OF ANASTOMOTIC LEAK. In: Endoscopy [Internet]. Georg Thieme Verlag KG; 2022. Available from: http://dx.doi.org/10.1055/s-0042-1745095
197. Dai YY, Gretschel S, Dudeck O, Rau B, Schlag PM, Hünerbein M. Treatment of oesophageal anastomotic leaks by temporary stenting with self-expanding plastic stents. British Journal of Surgery. 2009 Jul 9; 96(8):887–91.
198. Graziosi L, Marino E, Donini A. Stent Placement in the Management of Esophageal Leaks. The Annals of Thoracic Surgery. 2016 Nov; 102(5):1762–3.
199. Schaheen L, Blackmon SH, Nason KS. Optimal approach to the management of intrathoracic esophageal leak fo llowing esophagectomy: a systematic review. The American Journal of Surgery. 2014 Oct; 208(4):536–43.
204. Yeroushalmi KJ, Subhani M, Rizvon K. Successful Endoscopic Esophageal Stent Placement for Esophageal Anasto motic Leak. American Journal of Gastroenterology. 2018 Oct; 113(Supplement):S1633.
205. Lorenzo-Zúñiga V, Moreno-de-Vega V, Marín I, Boix J. Biodegradable stents in gastrointestinal endoscopy. World J Gastroenterol. 2014 Mar 7; 20(9):2212–7.
206. Papadakos SP, Argyrou A, Katsaros I, Lekakis V, Mpouga G, Vergadis C, et al. The Impact of EndoVAC in Addressing Post-Esophagectomy Anastomotic Leak in Esophageal Cancer Management. JCM. 2024 Nov 25; 13(23):7113.
207. Seika P, Biebl M, Raakow J, Berndt N, Feldbrügge L, Maurer MM, et al. The Association between Neoadjuvant Radio-Chemotherapy and Prolonged Healing of Anastomotic Leakage after Esophageal Resection Treated with EndoVAC Therapy. JCM. 2022 Aug 16; 11(16):4773.
208. Heits N, Bernsmeier A, Reichert B, Hauser C, Hendricks A, Seifert D, et al. Long-term quality of life after endovac-therapy in anastomotic leakages after esophagectomy. J Thorac Dis. 2018 Jan; 10(1):228–40.
209. Pattynama LMD, Pouw RE, Henegouwen MIVB, Daams F, Gisbertz SS, Bergman JJGHM, et al. Endoscopic vacuum therapy for anastomotic leakage after upper gastrointestinal surgery. Endoscopy. 2023 Nov; 55(11):1019–25.
226. Karimi P, Islami F, Anandasabapathy S, Freedman ND, Kamangar F. Gastric Cancer: Descriptive Epidemiology, Risk Factors, Screening, and Prevention. Cancer Epidemiology, Biomarkers & Prevention. 2014 May 1; 23(5):700–13.