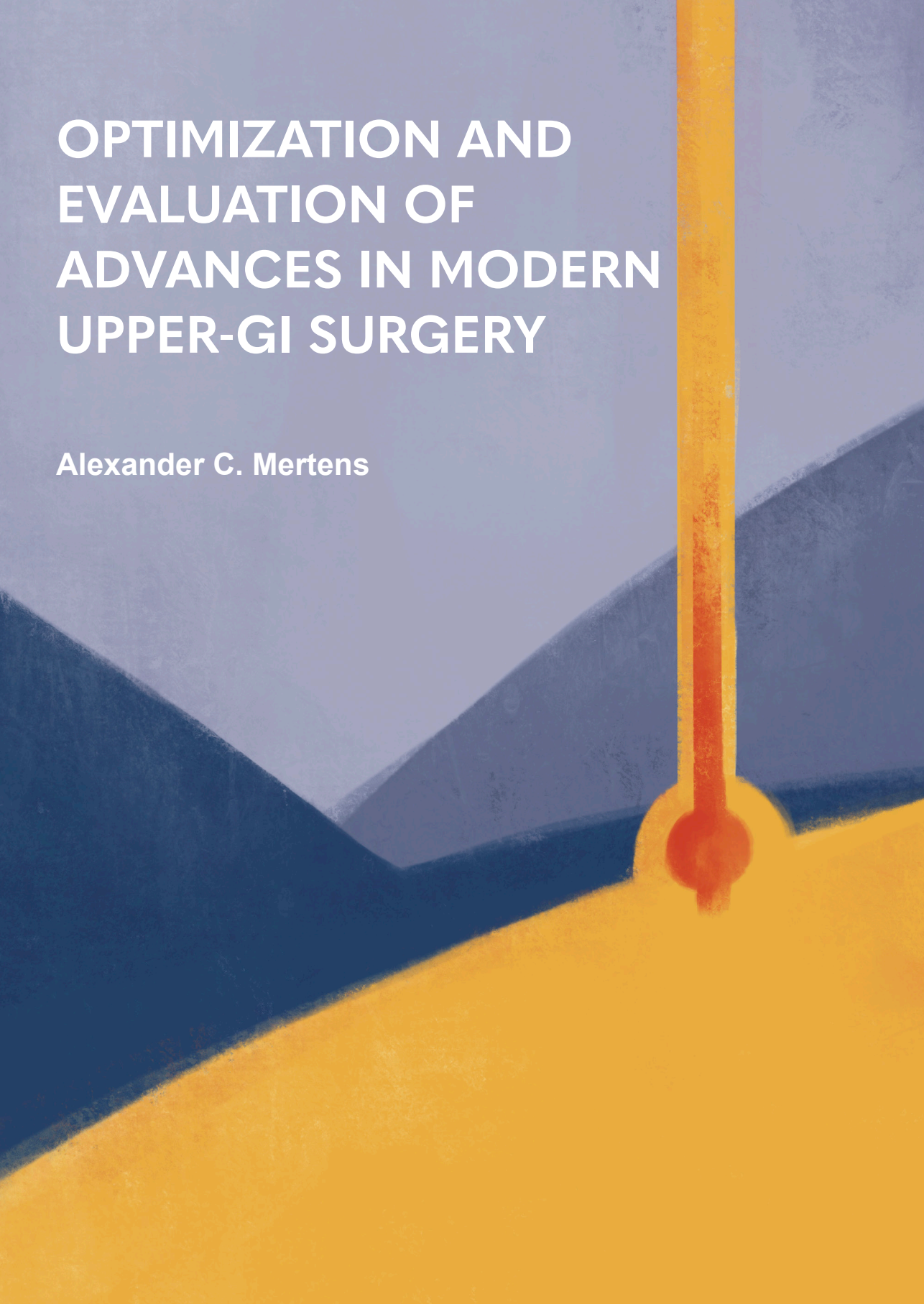


OPTIMIZATION AND EVALUATION OF ADVANCES IN MODERN UPPER-GI SURGERY

Alexander C. Mertens



OPTIMIZATION AND EVALUATION OF ADVANCES IN MODERN UPPER-GI SURGERY

Alexander C. Mertens

OPTIMIZATION AND EVALUATION OF ADVANCES IN MODERN UPPER-GI SURGERY

PROEFSCHRIFT

ter verkrijging van
de graad van doctor aan de Universiteit Twente,
op gezag van de rector magnificus,
prof. dr. ir. A. Veldkamp,
volgens besluit van het College voor Promoties
in het openbaar te verdedigen
op vrijdag 30 juni 2023 om 14.45 uur

door

Alexander Christiaan Mertens

geboren op 10 januari 1989
in Schiedam, Nederland

Dit proefschrift is goedgekeurd door:

De promotoren:

Prof. dr. IAMJ Broeders

Prof. dr. MI Van Berge Henegouwen

De copromotor:

Dr. WA Draaisma

Cover design: Jialei Ding

Printed by: Gildeprint

Lay-out: AC Mertens

ISBN (print): 978-90-365-5544-9

ISBN (digital): 978-90-365-5545-6

URL: <https://doi.org/10.3990/1.9789036555456>

© 2023 AC Mertens, Zeist, The Netherlands. All rights reserved. No parts of this thesis may be reproduced, stored in a retrieval system or transmitted in any form or by any means without permission of the author. Alle rechten voorbehouden. Niets uit deze uitgave mag worden vermenigvuldigd, in enige vorm of op enige wijze, zonder voorafgaande schriftelijke toestemming van de auteur.

PROMOTIECOMMISSIE:

Voorzitter/secretaris: prof.dr. J.N. Kok

Promotoren: prof. dr. IAMJ Broeders

Universiteit Twente, EEMCS, Robotics and Mechatronics

prof. dr. MI Van Berge Henegouwen

Amsterdam UMC

Copromotor: dr. WA Draaisma

Jeroen Bosch Ziekenhuis

Leden: prof.dr. T.J.M. Ruers

Universiteit Twente, TNW, Nanobiophysics

prof.dr. R.H. Geelkerken

Universiteit Twente, TNW, Multi-Modality Medical Imaging

prof. dr. E. Hazebroek

Universiteit Wageningen

prof. dr. R. van Hillegersberg

Universiteit Utrecht

dr. V.B. Nieuwenhuijs

Isala ziekenhuis Zwolle

dr. S.S. Gisbertz

Amsterdam UMC

TABLE OF CONTENTS

Chapter One	General introduction and outline of the thesis	1
PART I - BENIGN DISEASE		
Chapter two	Adverse Events in Robotic Assisted Hiatal Hernia Repair	17
Chapter three	Redo Hiatal Hernia Surgery: Robotic Laparoscopic Approach	33
Chapter four	Perfusion effects of ligation of the gastrosplenic ligament during antireflux surgery: a feasibility study on near-infrared imaging	47
Chapter five	Morbidity and mortality in complex robot-assisted hiatal hernia surgery: 7-year experience in a high-volume center	61
Chapter six	Operating times in robot-assisted surgery: let's move on	83
Chapter seven	Value of computed tomography in patients with failed antireflux surgery: Is CT all we need?	101
PART II - MALIGNANT DISEASE		
Chapter eight	Morbidity and mortality after curative gastrectomy in elderly patients: More harm than good?	117
Chapter nine	Treating early delayed gastric tube emptying after esophagectomy with pneumatic pyloric dilation	133
Chapter ten	Transthoracic versus transhiatal esophagectomy for esophageal cancer: a nationwide propensity score-matched cohort analysis	147
Chapter eleven	Gastrectomy versus Esophagectomy For Gastroesophageal junction Tumors: Short- And Long- term Outcomes From the Dutch Upper GI Cancer Audit	167
Chapter twelve	General discussion and future perspectives	193
APPENDICES		
Appendix I	Summary in Dutch / Nederlandse samenvatting	211
Appendix II	List of publications	223
Appendix III	Acknowledgements	227
Appendix IV	Curriculum Vitae Auctoris	235

CHAPTER ONE

General introduction and outline of the thesis

A.C. Mertens



GENERAL INTRODUCTION

Surgical procedures for Upper Gastro-Intestinal disease can be roughly divided in two major fields; benign and malignant pathology. Both of these fields have seen an immense progress in the past decades. The first part of this thesis will describe several studies in benign disease, while the second will focus on malignancies.

Surgical treatment in general has moved from open surgery towards laparoscopic and even robotic-assisted surgery. Well-known examples of this are the laparoscopic cholecystectomy and robot-assisted prostatectomy. This progress has not been without major setbacks. The first laparoscopic surgical procedures had a higher mortality than open surgery, but it has since come a long way. In recent years, laparoscopic surgery has become the standard access method for many routine procedures. For some more complex procedures, the preferred surgical approach has even started to shift towards robotic assisted surgery.

An open procedure allows the surgeon direct access and the best feel for the state of the tissue, although it results in more tissue damage. In experienced hands, laparoscopic surgery allows the surgeon to operate through small incisions at the cost of limited dexterity. Robotic assisted surgery restores intricate and precise movements to the surgeons' toolkit, while still having the advantage of keyhole surgery. The tradeoffs of robotic assisted surgery are the complete lack of tactile feedback, generally a longer operating time and higher costs: limitations that are slowly being resolved¹⁻³.

Along with a change in the materials used in surgical procedures and the improved outcomes of modern surgery, focus has been shifting from resolving mechanical or pathological issues to maximizing the long-term effects of treatment along with improving quality of life.

BENIGN UPPER GI SURGERY

Although gastroesophageal reflux disease (GERD) is a serious disease in and of itself, this thesis focusses on patients with a hiatal hernia as the suspected underlying cause of their complaints. In the normal anatomical situation, the LES lines up with an aperture in the diaphragm. The diaphragm provides external pressure on the esophagus, assisting the LES in its function.

ACID REFLUX AND HIATAL HERNIA SURGERY

Gastroesophageal reflux disease (GERD) is a debilitating spectrum of diseases of the stomach and esophagus, which the Montreal definition⁴ describes as follows: "GERD is a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications". It is estimated that up to 20% of the adult European population suffers from reflux at least weekly⁵. Common symptoms include nausea, heartburn and regurgitation, although severe cases can include symptoms such as dysphagia and even dental erosion. Apart from these very impactful but benign symptoms, acid exposure of the esophagus can also lead to strictures, ulcers and even malignancy⁶.

In the normal situation, the lower esophageal sphincter (LES) prevents gastric contents from entering the esophagus in large quantities, relaxing on demand to allow food to pass and excess gas to escape from the stomach. The diagnosis of GERD can be made based on a combination of typical symptoms and objectively confirmed changes such as mucosal breaks on endoscopy, evidence of Barrett's esophagus, peptic strictures in the absence of malignancy or positive pH-metry⁷.

Medication alone is sufficient to treat GERD in the vast majority of cases⁸. The estimated 5% of patients that do not achieve long-term control of GERD have to look for alternatives such as endoscopic or surgical treatment⁷.

DIAPHRAGMATIC HIATAL HERNIAS

Although GERD is a serious disease in and of itself, this thesis focusses on patients with a hiatal hernia as the suspected underlying cause of their complaints. In the normal anatomical situation, the LES lines up with an aperture in the diaphragm. The diaphragm provides external pressure on the esophagus, assisting the LES in its function.

SURGICAL APPROACH

In patients with a hiatal hernia and GERD, surgical treatment is often the preferred treatment method. It is worth noting that there is a patient group that has a hiatal hernia but is asymptomatic. In these patients without symptoms, surgical treatment aimed at restoring the native anatomy should be discouraged as the risk of serious

disease later in life is very small, in contrast to complications and side effects of surgery. If the symptoms of a hiatal hernia are serious enough to warrant the surgical risk, treatment should be considered. The efficacy of surgical treatment is high, with reported success rates of up to 90% and very low complication rates in specialized centers¹⁰⁻¹².

Regardless of the chosen surgical approach, the hiatal hernia repair for reflux disease broadly consists of three steps¹³. The abdominal contents that herniate through the hiatus are covered in the peritoneum, forming the hernia sac. If a hernia exists for long enough, the peritoneum often adheres to the diaphragm and intrathoracic organs. In these cases, the surgeon has to free the hernia sac from the surrounding organs. After this is completed, the herniated tissue can be repositioned in the abdomen and the hiatus can be narrowed in order to prevent a recurrence. After the hiatal hernia repair, surgeons nowadays also construct a fundoplication.

A fundoplication is constructed by wrapping a part of the stomach around the esophagus. There are multiple ways to perform the surgery. Roughly, there are two types of funduplications: complete and partial. In a complete fundoplication, the wrap covers the esophagus 360 degrees. Research shows that this leads to the best reflux control, at the cost of a higher incidence of symptoms like dysphagia. Partial wraps are generally classified as 270, 180 or 90 degrees. With decreasing coverage of the esophagus the chance of dysphagia becomes lower, but the efficiency of reflux control suffers as well. The wrap forms a bulk that, in addition to the sutures that fixate the fundoplication to the diaphragm, prevents recurrent herniation.

Unfortunately, despite all precautions, up to 40% of patients experience a recurrent hernia¹⁴⁻¹⁷, often within the first five years^{7,18}. In these patients, surgical treatment becomes exponentially harder than the initial repair due to adhesions forming as a result of tissue trauma from the initial procedure. Fortunately, redo surgery is not always needed, as there are many asymptomatic recurrences^{19,20}. In patients that do require redo surgery, consensus states that it is possible to perform a redo procedure 2 to 3 times with increasing risks and lowering satisfaction rates²¹⁻²³.

MALIGNANT UPPER GI SURGERY

The second part of this thesis describes studies regarding malignant disease of the esophagus and stomach.

ESOPHAGEAL AND GASTROESOPHAGEAL JUNCTION CANCER

Esophageal cancer is the eighth most common malignancy worldwide^{24,25}. In recent years, this disease has been found to increase in incidence. This information is all the more worrying when considering the average 5-year overall survival for all types of esophageal cancer of around 50% after multimodal therapy^{24,25}.

While neoadjuvant treatment has been introduced with increasing rates of success, surgical resection is still the cornerstone of curative treatment for any but the earliest stages of esophageal cancer or patients that do not want – or are unfit for undergoing - surgical treatment²⁶. For this last category of patients, definitive chemoradiotherapy is an option, although this treatment has less favorable outcomes. In early localized disease, endoscopic resection can be an option for a select group of patients.

SURGICAL TREATMENT OPTIONS

In carcinoma of the mid to lower third of the esophagus and the esophagogastric junction, both a transthoracic resection with a one-, two- or three field lymphadenectomy or a transhiatal approach with limited lymphadenectomy can be performed. These procedures can be performed in an open, minimally invasive, robotic assisted or hybrid fashion, with a choice between a cervical or intrathoracic anastomosis. Lastly, there is an additional choice between an intrathoracic or cervical anastomosis.

Depending on the length of the resected portion of the esophagus, the anastomosis can be made intrathoracically or cervically. If the tumor is located more proximally, or a transhiatal resection is performed, it is not possible to simply pull the stomach up to meet the resection margin of the esophagus since the vessels and other tissues that connect to the stomach do not provide sufficient slack. Whenever possible, the stomach will be adapted to create a gastric tube that is longer than the original stomach and can bridge the gap.

Transthoracic esophagectomy is known for its more radical resection due to the en-bloc resection of the esophagus with an extensive intrathoracic lymph node dissection^{27,28}, compared to the more limited lymph node dissection in the transhiatal approach²⁹. Research has failed to prove a clear superiority of one of these approaches.

Although the transthoracic approach provides a more extensive resection in terms of a higher lymph node yield, the transhiatal procedure is associated with shorter hospital stay and decreased short term mortality and morbidity³⁰⁻³³. Recent research suggests a link between a higher lymph node yield and long-term survival^{34,35}, although there are several conflicting publications on this subject^{31,36-40}. While there is a general consensus on the metrics for an adequate resection, it is hard to quantify which factor contributes the most to a patients' recovery. It could be the circumferential resection margin, R0 versus R+ resection, the number of resected lymph nodes or even the location of the resected lymph nodes.

Neoadjuvant chemoradiation according to the CROSS26 regimen has been the nationally accepted standard for resectable (cT2-4aN0-3M0 and T0-1N+M0) esophageal carcinoma in the Netherlands since 2010. Internationally, many different protocols are in use.

POSTOPERATIVE QUALITY OF LIFE AND DELAYED GASTRIC TUBE EMPTYING

It is estimated that 11-50% of patients that undergo a gastric tube reconstruction get affected by delayed gastric emptying, depending on the definition used⁴¹⁻⁴⁶. This finding can be defined as a distension of the gastric tube. It can have a severe impact on the quality of life, as the hospital admission can be prolonged and oral intake can be impossible or highly uncomfortable. Frequently reported symptoms are loss of appetite, reflux, dysphagia and even regurgitation. There are various treatments available, although most are temporary or symptomatic.

Although the exact factors responsible may be unknown, studies have shown that the quality of treatment has been going up. The 5-year survival rate of non-metastatic esophageal adenocarcinoma has increased from 12% just 30 years ago, to 47% with neoadjuvant treatment in 2015. At the same time, the in-hospital, short-term mortality and incidence of anastomotic leakage have dropped significantly^{47,48}. Since there is no definitive evidence regarding the best surgical treatment in terms of survival, quality of life after surgery plays a significant role in the choice of therapy. Finding the optimal balance between an adequate resection while retaining the maximum attainable postoperative quality of life is very important in the decision-making process.

AIM OF THIS THESIS

Surgery is a medical field that depends greatly on intuition and experience in addition to thorough scientific research. This often leads to innovative treatment methods, which need to be proven over time. This thesis aims to explore and evaluate the current standard of care in upper gastrointestinal surgery for both benign and malign disease, and build on this with evaluating innovative diagnostic and therapeutic methods. The topics and points of discussion described in this introduction provide the basis for the studies included in this thesis.

BENIGN DISEASE

Part I of this thesis will explore the surgical treatment and advances of surgical treatment of diaphragmatic hiatal hernias.

The safety and risks of hiatal hernia surgery are described in chapter five. Any surgery carries risk, and even if increasingly rare, surgeons should be prepared to deal with these. Chapter two discusses the adverse events that might be encountered during robot-assisted hiatal hernia surgery. Chapter three explains how to handle the recurrence of a hiatal hernia, including thoughts on one of the most important aspects of benign disease: when not to operate. Chapter six discusses the merits of an often-reported criticism of robotic assisted surgery: cost. During surgery, it is often necessary to disrupt healthy tissue in order to carry out a repair elsewhere. Chapter four explores the incidence of damage to the spleen due to ligation of vasculature during the creation of a fundoplication. Creating a surgical plan often requires preoperative imaging. Chapter seven evaluates the accuracy of CT-imaging compared to intraoperative findings.

MALIGNANT DISEASE

Part II of this thesis will discuss a subset of the treatment options and epidemiologic factors relevant in esophageal and gastric malignant disease.

In esophageal cancer there is consensus that the diseased esophagus should be removed, in addition to the gastroesophageal junction. In gastric cancer, however, it is often harder to discern exactly where the tumor are located and there is active discussion on the optimal type of resection for each location. It gets especially complicated when the tumor in question is located at the gastro-esophageal junction, because in this situation there often is overlap between gastric, esophageal, and gastro-esophageal junction treatment options and guidelines. Chapter eleven uses data from a national registry (DUCA; Dutch Upper GI Cancer Audit) to attempt to compare these two approaches. Surgeons have the option of performing an esophageal resection through a transhiatal or transthoracic approach. Chapter ten compares these two approaches using a Dutch national cancer treatment

audit registry. After an esophagectomy, the gastro-intestinal tract needs to be reconstructed. This is generally done through a gastric tube reconstruction. Chapter nine describes the results of a case series in patients with early postoperative delayed gastric tube emptying, in which an endoscopic pneumatic pyloric dilation procedure was performed. The chapter discusses the safety and gains in quality of life in this population. In chapter eight, the Dutch research database of the LOGICA Study Group for gastric cancer was used to attempt to determine the amount of risk a patient is exposed to after surgical resection, depending on their age.

REFERENCES

1. Hanly EJ, Talamini MA. Robotic abdominal surgery. *Am J Surg.* 2004 Oct;188(4A Suppl):19S-26S.
2. Braumann C, Jacobi CA, Menenakos C, et al. Robotic-assisted laparoscopic and thoracoscopic surgery with the da Vinci system: a 4-year experience in a single institution. *Surg Laparosc Endosc Percutan Tech.* 2008 Jun;18(3):260–6.
3. Broeders IAMJ. Robotics: The next step? *Best Pract Res Clin Gastroenterol.* 2014;28(1):225–32.
4. Vakil N, Van Zanten S V., Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: A global evidence-based consensus. Vol. 101, *American Journal of Gastroenterology.* Am J Gastroenterol; 2006.
5. Dent J, El-Serag HB, Wallander MA, et al. Epidemiology of gastro-oesophageal reflux disease: A systematic review. Vol. 54, *Gut.* Gut; 2005 [cited 2021 Apr 24]. p. 710–7.
6. Coleman HG, Xie SH, Lagergren J. The Epidemiology of Esophageal Adenocarcinoma. *Gastroenterology.* 2018 Jan 1;154(2):390–405.
7. Stefanidis D, Hope WW, Kohn GP, et al. Guidelines for surgical treatment of gastroesophageal reflux disease. *Surg Endosc.* 2010 Nov 20;24(11):2647–69.
8. Klinkenberg-Knol EC, Nelis F, Dent J, et al. Long-term omeprazole treatment in resistant gastroesophageal reflux disease: Efficacy, safety, and influence on gastric mucosa. *Gastroenterology.* 2000 Apr 1;118(4):661–9.
9. Robinson B, Dunst CM, Cassera MA, et al. 20 years later: laparoscopic fundoplication durability. *Surg Endosc.* 2015 Sep 9;29(9):2520–4.
10. Luketich JD, Nason KS, Christie NA, et al. Outcomes after a decade of laparoscopic giant paraesophageal hernia repair. *J Thorac Cardiovasc Surg.* 2010 Feb;139(2):395–404, 404.e1.
11. Banki F, Kaushik C, Roife D, et al. Laparoscopic Repair of Large Hiatal Hernia Without the Need for Esophageal Lengthening With Low Morbidity and Rare Symptomatic Recurrence. *Semin Thorac Cardiovasc Surg.* 2017;29(3):418–25.
12. Tolboom R, Broeders I, Draaisma W. Robot-Assisted Laparoscopic Hiatal Hernia and Antireflux Surgery. *J Surg Oncol.* 2015 Sep;112(3, SI):266–70.
13. Oelschläger BK, Pellegrini CA, Hunter J, et al. Biologic Prosthesis Reduces Recurrence After Laparoscopic Paraesophageal Hernia Repair. *Trans . Meet Am Surg Assoc.* 2006;124:146–55.
14. Sathasivam R, Bussa G, Viswanath Y, et al. 'Mesh hiatal hernioplasty' versus 'suture cruroplasty' in laparoscopic para-oesophageal hernia surgery; a systematic review and meta-analysis. *Asian J Surg.* 2019 Jan;42(1):53–60.
15. Asti E, Lovece A, Bonavina L, et al. Laparoscopic management of large hiatus hernia: five-year cohort study and comparison of mesh-augmented versus standard crura repair. *Surg Endosc.* 2016 Dec 29;30(12):5404–9.
16. Zhang C, Liu D, Li F, et al. Systematic review and meta-analysis of laparoscopic mesh versus suture repair of hiatus hernia: objective and subjective outcomes. *Surg Endosc.* 2017 Dec;31(12):4913–22.

17. Mittal SK, Bikhchandani J, Gurney O, et al. Outcomes after repair of the intrathoracic stomach: objective follow-up of up to 5 years. *Surg Endosc.* 2011 Feb 10;25(2):556–66.
18. Dunne N, Stratford J, Jones L, et al. Anatomical failure following laparoscopic antireflux surgery (LARS): does it really matter? *Ann R Coll Surg Engl.* 2010 Mar;92(2):131–5.
19. Donkervoort SC, Bais JE, Rijnhart-de Jong H, et al. Impact of anatomical wrap position on the outcome of Nissen fundoplication. *Br J Surg.* 2003 Jul;90(7):854–9.
20. Chen Z, Zhao H, Sun X, et al. Laparoscopic repair of large hiatal hernias: clinical outcomes of 10 years. *ANZ J Surg.* 2018;88(10):E703–7.
21. Zahiri HR, Weltz AS, Sibia US, et al. Primary versus redo paraesophageal hiatal hernia repair: a comparative analysis of operative and quality of life outcomes. *Surg Endosc.* 2017 Dec 10;31(12):5166–74.
22. Mertens AC, Tolboom RC, Zavrtnik H, et al. Morbidity and mortality in complex robot-assisted hiatal hernia surgery: 7-year experience in a high-volume center. *Surg Endosc.* 2019 Jul 22;33(7):2152–61.
23. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin.* 2015 Mar;65(2):87–108.
24. IKNL. Nederlandse Kankerregistratie (NKR). [cited 2018 Nov 20]. Available from: <https://www.cijfersoverkanker.nl>
25. Van Hagen P, Hulshof MCCM, Van Lanschot JJB, et al. Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer. *N Engl J Med.* 2012;366(22):2074–84.
26. McKeown KC. Total three-stage oesophagectomy for cancer of the oesophagus. *Br J Surg.* 1976 Apr;63(4):259–62.
27. Lewis I. The surgical treatment of carcinoma of the oesophagus; with special reference to a new operation for growths of the middle third. *Br J Surg.* 1946 Jul;34:18–31.
28. Orringer MB, Sloan H. Esophagectomy without thoracotomy. *J Thorac Cardiovasc Surg.* 1978 Nov;76(5):643–54.
29. Hulscher JBF, Van Sandick JW, De Boer AGEM, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. *N Engl J Med.* 2002;347(21):1662–9.
30. Boshier PR, Anderson O, Hanna GB. Transthoracic versus transhiatal esophagectomy for the treatment of esophagogastric cancer: A meta-analysis. *Ann Surg.* 2011;254(6):894–906.
31. Wolff CS, Castillo SF, Larson DR, et al. Ivor Lewis approach is superior to transhiatal approach in retrieval of lymph nodes at esophagectomy. *Dis Esophagus.* 2008;21(4):328–33.
32. van der Werf LR, Dikken JL, van Berge Henegouwen MI, et al. A Population-based Study on Lymph Node Retrieval in Patients with Esophageal Cancer: Results from the Dutch Upper Gastrointestinal Cancer Audit. *Ann Surg Oncol.* 2018;25(5):1211–20.
33. Visser E, Rossum PSNV, Ruurda JP, et al. Impact of Lymph Node Yield on Overall Survival in Patients Treated with Neoadjuvant Chemoradiotherapy Followed by Esophagectomy for Cancer. *Ann Surg.* 2017;266(5):863–9.

34. Rizzetto C, DeMeester SR, Hagen JA, et al. En bloc esophagectomy reduces local recurrence and improves survival compared with transhiatal resection after neoadjuvant therapy for esophageal adenocarcinoma. *J Thorac Cardiovasc Surg.* 2008;135(6):1228–36.
35. Gockel I, Heckhoff S, Messow CM, et al. Transhiatal and transthoracic resection in adenocarcinoma of the esophagus: Does the operative approach have an influence on the long-term prognosis? *World J Surg Oncol.* 2005;3:1–11.
36. Grotenhuis BA, Van Heijl M, Zehetner J, et al. Surgical management of submucosal esophageal cancer: Extended or regional lymphadenectomy? *Ann Surg.* 2010;252(5):823–9.
37. Ovrebø KK, Lie SA, Laerum OD, et al. Long-term survival from adenocarcinoma of the esophagus after transthoracic and transhiatal esophagectomy. *World J Surg Oncol.* 2012;10:1–10.
38. Davies AR, Sandhu H, Pillai A, et al. Surgical resection strategy and the influence of radicality on outcomes in oesophageal cancer. *Br J Surg.* 2014;101(5):511–7.
39. Omloo JMT, Lagarde SM, Hulscher JBF, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. *Ann Surg.* 2007 Dec;246(6):992–1000; discussion 1000-1.
40. Sutcliffe RP, Forshaw MJ, Tandon R, et al. Anastomotic strictures and delayed gastric emptying after esophagectomy: Incidence, risk factors and management. *Dis Esophagus.* 2008;21(8):712–7.
41. Gockel I, Gönner U, Domeyer M, et al. Long-term survivors of esophageal cancer: Disease-specific quality of life, general health and complications. *J Surg Oncol.* 2009 Oct 29;102(5):516–22.
42. McLarty AJ, Deschamps C, Trastek VF, et al. Esophageal Resection for Cancer of the Esophagus: Long-Term Function and Quality of Life. *Ann Thorac Surg.* 1997 Jun;63(6):1568–71.
43. Benedix F, Willems T, Kropf S, et al. Risk factors for delayed gastric emptying after esophagectomy. *Langenbeck's Arch Surg.* 2017 May 21;402(3):547–54.
44. Anandavadevelan P, Wikman A, Johar A, et al. Impact of weight loss and eating difficulties on health-related quality of life up to 10 years after oesophagectomy for cancer. *Br J Surg.* 2018 Mar;105(4):410–8.
45. Deldycke A, Van Daele E, Ceelen W, et al. Functional outcome after Ivor Lewis esophagectomy for cancer. *J Surg Oncol.* 2016 Jan;113(1):24–8.
46. Shapiro J, van Lanschot JJB, Hulshof MCCM, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): Long-term results of a randomised controlled trial. *Lancet Oncol.* 2015 Sep 1;16(9):1090–8.
47. Slaman AE, Pirozzolo G, Eshuis WJ, et al. Improved Clinical and Survival Outcomes After Esophagectomy for Cancer Over 25 Years. *Ann Thorac Surg.* 2022;114(4).

PART I

Benign disease



CHAPTER TWO

Adverse Events in Robotic Assisted Hiatal
Hernia Repair

AC Mertens, IAMJ Broeders

Robotic Assisted Hernia Repair, 2019



INTRODUCTION

Surgery for benign conditions, such as hiatal hernias, should have a low complication risk since in the vast majority of cases the goal of the procedure relates to quality of life while the health risk of conservative treatment is limited.

Antireflux surgery and procedures for hiatal hernia have been associated with high risk of morbidity and mortality and moderate subjective outcomes. The majority of information still leans on the evidence from the era of open surgery where these types of procedures were performed by many general surgeons, usually in low volume. Currently, laparotomy has been replaced by minimally invasive surgery and postoperative care has improved drastically. Surgeons have become aware of the importance of excellent knowledge of hiatal anatomy and the essential concepts of hiatal closure and anti-reflux procedures. An increase in referrals seems to parallel the concentration of surgical care. Nonetheless, surgery for large hiatal hernias and reoperative procedures can be very challenging making the awareness of potential risks essential.

In this chapter we will describe the possible adverse events in hiatal hernia surgery. We will try to explore why these events occur and the possible treatment options for when they do. We will divide this chapter in intraoperative, postoperative/in-hospital and late adverse events.

INTRAOPERATIVE ADVERSE EVENTS IN HIATAL HERNIA SURGERY

Intraoperative complications may relate to bleeding, organ perforation and damage to vagal nerves or intrathoracic structures. We will not discuss the complications related to pneumoperitoneum as these have to be considered in any laparoscopic and robot assisted procedure.

BLEEDING

The most common bleeding in laparotomy is caused by traction on the spleno-gastric ligament, resulting in splenic capsule tears or bleeding from the short gastric vessels. Splenectomy in hiatal hernia repair was not uncommon in the past and contributed to the unfavourable reputation to of these procedures. Today, the open approach to hiatal hernia surgery and fundoplication is outdated and should be strongly discouraged. Splenectomy has become rare due to the growing experience with laparoscopic techniques and the available equipment.

In the case of 270° and 360° fundoplication, avoidance of traction on the gastric fundus prevents injury to the short gastric vessels. It is most advisable to use a

“high-tech” sealing and cutting device, such as an ultrasonic dissector, advanced bipolar sealing device or the robotic vessel sealer. In the case of bleeding originating from the short gastric vessels, damage can be controlled with these devices. A suction device should be on the table, or at the very least be quickly accessible at all times. Bleeding from small splenic capsule tears should be treated by gauze compression; these gauzes should be left for several minutes to allow for natural clotting to occur. If there is persistent bleeding, a resorbable gauze of surgeon preference can be applied on the splenic surface and left in situ.

Bothersome hemorrhage may also arise during dissection of the hernia sac and esophagus. Surgery usually starts with the incision of the gastro-hepatic ligament. This ligament often harbours a large aberrant artery supplying the left lobe of the liver. If possible, this artery should be spared, but this may be troublesome in big hiatal hernias. Alternatively, it can be ligated, but advanced sealing or clips such as Hem-o-lock® (Weck® Morrisville, NC) should be used in all instances to avoid serious bleeding. In large hiatal hernias special care is required for the left gastric artery or vein as these may project onto the operation field due to migration of the stomach towards the mediastinum.

Usually, the vena cava is out of the way, but one should always check its position before dissection or suturing of the crus. It can easily be visualized by lifting the caudate lobe of the liver. The vena cava can get close to the hiatal hernia in reoperative surgery due to scarring, and/or due to the need to apply traction on the hiatal pillars when approximating the crus. In the case of a small puncture, bleeding may be limited. Quick and careful suturing with a permanent polypropylene suture is possible. While preparing for suturing, a gauze should be applied at the site of injury to prepare for repair and avoid the occurrence of a massive pulmonary embolism with the insufflated CO₂. Surgeons attempting vena cava repair should possess excellent laparoscopic suturing skills.

In case of large tears and massive bleeding, immediate gauze compression should be applied. This is usually sufficient for controlling the bleeding due to the low pressure in the venous system. The patient can then be prepared for laparotomy and surgical support by a vascular surgeon can be arranged.

Other vascular structures that require awareness are the left and right diaphragmatic arteries and the inferior phrenic vein, which are always visible approximately one centimeter above the upper margin of the hiatal opening. Phrenic arteries can be damaged during dissection of the gastro-phrenic ligament or during crural reapproximation. Control is gained by sealing, or simply with tying the approximating sutures in hiatal repair.

In esophageal dissection, one may encounter small aorto-esophageal branches. Cutdown by sealing or diathermy is advised, while maintaining a safe distance from the esophagus and vagal nerve branches. If there is hemorrhage, a no touch approach or gauze compression is advisable to avoid thermal damage to essential structures. This type of bleeding is usually low volume and self-limited.

Special attention is required for the aorta when suturing the diaphragmatic crus. Especially in large type 3 and 4 hiatal hernias, the left crus can be stretched over the distal end of the thoracic aorta. The first two to three sutures below the esophagus should be positioned with great care and subtle needle handling to avoid puncturing of the aorta. One may lift the left crus or push it to the patients left with the left-hand needle driver to create space between the limb and the aorta. In case of injury to the aorta with subsequent bleeding, the surgeon should carefully remove the needle by pulling on the suture and maintain direct compression of the crus on the aorta with a needle driver followed by gauze compression. Puncture holes will stop bleeding within minutes and a just compress approach is highly advisable. In case the aorta is punctured, do not continue suturing and knot tying, because the needle path through the aorta is unknown and knot tying may result in an aortic tear with consequent massive bleeding.

ORGAN PERFORATION

Perforation of the small intestine and large bowel should be avoided by utilizing correct laparoscopic techniques. In robot assisted surgery, special care is required when exchanging instruments because the intestine could potentially move into a position in front of the ends of the trocar, resulting in a risk of injury when exchanging instruments blindly. Likewise, great care should be taken when moving robotic instruments outside the field of view. Recognized intestinal perforations or serosal tears should be sutured immediately to avoid real or potential contamination with intestinal content.

Gastric perforation may result from excessive traction with robotic instruments. The exerted forces can be high and increase when the size of the instrument tip diminishes. This risk is enhanced due to the absence of haptic feedback. The bigger the hernia, the larger the risk. Extreme reverse Trendelenburg position is very helpful in repositioning the hernia contents, because gravity will assist the spontaneous repositioning of an intrathoracic stomach.

Serosal tears of the stomach surface or superficial muscular tears need no repair. Transmural or deep tears should be closed immediately to avoid unnecessary spillage of content. A barbed suture is very helpful in closing these lacerations. At the end of the procedure the sutured area should be inspected again because extensive manipulation of the stomach may cause suture line dehiscence.

Small or microscopic gastric perforations may also result from fundoplication “takedown” during reoperative surgery, especially when removing previously placed sutures. If this occurs, an effort should be made when possible to cover this dissected area with the newly created fundoplication to protect this vulnerable surface.

Esophageal perforation is one of the most disastrous complications. It should be avoided at all times by careful dissection of the esophagus. Excessive traction is undesirable and dissection of the hernia sac from the gastro-oesophageal junction should be avoided because the anatomy can be unclear, putting both the distal esophagus and vagal nerves at risk. One can simply leave the hernia sac in the abdomen attached to the gastro-esophageal junction after the hiatal hernia repair and fundoplication. Most of it will atrophy in due time.

Special care is needed for gastric and esophageal dissection in reoperative surgery. The exact anatomy may be difficult to ascertain during dissection and adhesions can be very dense; especially at the dorsal side of the esophagus and stomach. Prior use of mesh for crural reinforcement may greatly increase the difficulty of dissection. In the worst case scenario, the procedure should be aborted but this is an infrequent occurrence. Conversion to laparotomy can be considered when the surgeon believes that manual or hand assisted release of adhesions may result in a better outcome.

Any recognized esophageal perforation should be closed and covered with the gastric wall in the subsequent fundoplication. If this occurs, we recommend the performance of an esophageal contrast swallow X-ray or a CT scan with oral contrast that day or the next day to rule out any leakage of intestinal content.

DAMAGE TO VAGAL NERVES AND INTRATHORACIC STRUCTURES

The pleura usually needs to be dissected from the hernia sac in big hiatal hernias. This may result in pleural tears which are usually easily noticed. The pleurae are especially at risk in reoperative surgery, and damage may be unavoidable. The pulmonary parenchyma will hardly ever incur injury and one should not attempt to close pleural defects.

The anesthesiologist should be asked to check end-expiratory pressure and induce a post expiration end pressure (PEEP) exceeding the intra-abdominal pressure induced by the CO₂ pneumoperitoneum if the pleural tear results in significant physiologic changes. The surgeon may lower CO₂ pressure, in combination with adequate muscle relaxation. PEEP should be maintained until the surgeon uses suction to remove as much CO₂ as possible when removing the trocars¹. A clinically significant pneumothorax will rarely result, but a chest X-ray is advisable in the recovery room.

A small-bore pleural drain may be introduced in the case of pulmonary collapse such as a tension pneumothorax, although this is rarely necessary.

Pericardial and pulmonary veins can be differentiated when removing the hernia sac and dissecting the esophagus to create sufficient intra-abdominal length. Damage can be avoided at all times with careful and mostly gentle blunt dissection. Hernia sac dissection should be performed initially at the outer surface of the sac. This will facilitate blunt dissection for effective extraction of the sac from the mediastinum and avoid damage to mediastinal structures while minimizing blood loss.

Pericardial or myocardial injury could result from hiatal closure in giant hernias or from gastropexy to the diaphragm²⁻⁴. One should be aware of this if the patient should develop a cardiac arrhythmia or a sudden drop in cardiac output. The pericardium may be opened through the hiatal opening, or through a small cutdown of the diaphragm adjacent to the pericardium. One should avoid the use of tackers for mesh fixation at all times in the vicinity of aorta, vena cava or pericardium. The surgeon should be aware of the position of these structures which are often (partly) covered by the diaphragm.

Vagal nerve injury with subsequent delayed gastric emptying is a feared complication of anti-reflux surgery and hiatal hernia repair. In primary surgery the anterior and posterior vagal nerves can generally be easily identified and spared. Damage to these nerves can lead to delayed gastric emptying, further aggravating the recovery of normal intake in patients undergoing a fundoplication with some patients experiencing a lack of improvement over time resulting in permanent intestinal difficulties. The reported incidence of accidental vagal nerve injury in the available literature is around 2%, although these numbers mainly describe the incidence in open surgery⁵⁻⁷. The actual percentage is potentially much higher.

Damage can be avoided by dissection of the esophagus at a distance from the crural opening, preferably with gentle blunt techniques. The use of energy devices should be limited to a safe distance from the esophagus. The posterior vagal nerve branch is especially at risk during dissection of the posterior portion of the hernia sac. We recommend lifting the vagal nerve together with the esophagus with an atraumatic instrument or with a flat soft drainage tube. The posterior vagal nerve branch is adjacent to the posterior surface of the esophagus, but may be found at a further distance in the mediastinum in giant hernias during sac dissection. It sometimes curves toward the area of the dissection at the level of the gastro-esophageal junction. Rarely, it can have more than one branch, making these especially vulnerable to injury.

The anterior vagal nerve branch is at risk when opening the mediastinum at the anterior side of the esophagus, especially in reoperative surgery. It may also be damaged during dissection of the hernia sac from the anterior surface of the esophagus.

The mediastinum should be opened as high as possible in the hiatus, and sac dissection should be attempted in a blunt fashion. When sharp dissection is necessary, it is recommended to initiate this dissection somewhat distally on the sac, away from the gastro-esophageal junction. Although initially this might require sharp dissection of the first layer, further dissection can be performed bluntly.

POSTOPERATIVE IN-HOSPITAL COMPLICATIONS

Robotic assisted hiatal hernia repair generally is a fairly sterile and safe operation⁸⁻¹³. Aside from the risk of surgical site infection present in any surgery, there is a small risk of gastro-intestinal organ perforation with accompanying infection. The most common sources of perforation are torn fundoplication sutures, laceration by a surgical instrument, trocar perforation or ischemic perforation. These sources of infection should be recognized and treated intraoperatively as described above. Thermal damage, both to the esophagus or stomach should be avoided by dissection at distance from the organ wall. Short gastric vessel division should be performed at least 0.5 centimeters away from the gastric border. In case of obvious thermal damage to the stomach wall, one can consider plication or resection with a linear endoscopic stapler.

As in any surgery, postoperative elevation of C-reactive protein or leukocyte count can be expected but a postoperative ileus is abnormal in hiatal hernia surgery. Severe gastric dilatation due to emptying disorders may occur and should be treated with a nasogastric tube perhaps combined with a jejunal feeding tube. Although most of these resolve in just a few days to weeks, some problems may not resolve.

When an intra-abdominal infection is suspected, we advise CT imaging as the primary diagnostic method due to its high specificity for the diagnosis of any free fluid. Perforation of the esophagus and/or stomach can be diagnosed using an orally administered contrast agent prior to scanning after performance a non-contrasted scan for reference.

Suspected gastric perforation should be treated by re-laparoscopy, perforation closure or partial gastric resection and drainage. When a perforation of the esophagus is diagnosed, endoscopic stenting can be used to close the defect as well as possible. Concomitant mediastinal collections and pleural empyema require immediate drainage. When possible, this can be performed by radiologic intervention but a thoracoscopic procedure or lateral thoracotomy may be required

for adequate drainage. This procedure often needs to be repeated several times in case of serious mediastinitis. Esophageal perforation can be treated with low mortality by continuous close and aggressive, often repetitive, invasive intervention. The hospital stay often takes numerous weeks and the time to full recovery is frequently over one year.

The development of an abscess may also occur without identification of an overt perforation. These abscesses are usually located in the mediastinum or just below the diaphragm on the left side. In the event that imaging studies do not reveal evidence of a perforation, percutaneous or laparoscopic drainage should be performed.

Moderate dysphagia is common after fundoplication and these complaints should diminish over time. As long as sufficient nutritional intake of any kind is assured, it is advisable to delay intervention for 6 to 8 weeks as these will commonly resolve without treatment.

When intake is impossible or highly painful, early intervention should be considered. The most common reasons for dysphagia during the in-hospital period are an overly tight repair and/or recurrent hiatal hernia. Several diagnostic options are available under those circumstances. If complaints are sufficient to consider a recurrent hiatal hernia, CT scanning should be considered using both oral and intravenous contrast. If the suspicion instead is a fundoplication that is too tight, a barium swallow is the preferred diagnostic tool.

In-hospital hernia recurrence or complete blockage of food and fluids should be treated within days. The area is well accessible in the first two weeks after surgery, and reoperative surgery can usually be performed laparoscopically, preferably with robotic assistance.

LATE COMPLICATIONS

Funduplications are designed to provide a one-way valve to prevent the reflux of gastric contents at the gastro-esophageal junction. Many side effects of this treatment are directly related to the function of this newly created valve function, one of which is the prevention of belching. In some patients this can be debilitating due to air trapping, with aerophagia or ingestion of carbonated drinks that will aggravate these symptoms. This side effect is usually called gas bloat and is accompanied with increased flatulence.

Postoperative treatment consists of efforts to prevent the entrance of air into the stomach. This is most easily managed by limiting the intake of carbonated drinks. In the case of true aerophagia, treatment is more involved due to the variety of etiologies of the problem, ranging from chewing gum to unconscious behavioral

traits or psychiatric problems. The most effective method to prevent gas bloating is operatively tailoring the fundoplication to the patient. Numerous high quality studies have proven the superiority of a partial fundoplication over a 360 Nissen fundoplication¹⁴⁻¹⁷, with equal long term reflux control and less gas bloating. Preoperative manometric testing will greatly aid in the preoperative decision making process for each patient regarding whether a partial or full fundoplication is most appropriate.

In the instance of a para-esophageal hernia, the anatomical defect is most likely the cause of problems, and an anterior fundoplication after hiatal hernia repair can be sufficient to avoid reflux. This fundoplication is closest to the normal anatomy and will usually result in physiologic reflux without bloating due to air trapping. Many studies have been published on this subject that report excellent long-term results.

Recurrent reflux after fundoplication is often a symptom of recurrent hiatal hernia, and should be considered when a prior successful repair has now failed to relieve reflux symptoms. Studies^{9,16,18-20} have identified that some form of radiologic recurrence is identified in 40%, symptomatic recurrence in 20% and reoperative surgery is necessary in 10% of patients. The use of mesh seems to result in less recurrence at the short term but has equivalent long-term results.

Patients may also complain of symptoms comparable to the preoperative situation, even in the absence of pathologic reflux. This often leads to the resumption of the use of antacid medication. In order to ascertain the correct etiology for the symptomatology there are several diagnostic tools available to identify the source of the situation including CT scanning, barium swallow and 24-hour esophageal pH-measurement. CT imaging is most valuable to confirm the development of a recurrent hiatal hernia and it will often have sufficient resolution to confirm a failed fundoplication. A barium swallow series can be useful for confirming gastro-esophageal reflux and can also indicate a significant hiatal hernia but, like CT scanning, does not reveal reflux over time. A 24-hour esophageal pH measurement provides the best evidence for recurrent reflux and is the investigational method of choice should there be a lack of demonstration of a failed prior repair as demonstrated by imaging techniques.

If a recurrent hiatal hernia or failed fundoplication is proven, the choice of treatment is up to the surgeon and more importantly, the patient. In some cases, reinstatement of acid suppression therapy will be sufficient, while in more severe cases another hiatal hernia repair with fundoplication will be required. It is important to note that patient satisfaction after reoperation decreases from 85-90% to 70%²⁰⁻²³. Reoperative surgery can be very challenging and should only be performed by surgeons with a high-volume reflux and hiatal hernia repair practice. The ability

to perform primary antireflux surgery does not mean that one has to be able to treat recurrence; referral to centers specialized in reoperative surgery is worthy of consideration.

The effects and complications of the use of mesh in hiatoplasty is a major source of controversy in the literature^{9,24}. There are many types and shapes of mesh, which can be categorized as follows; pledgets (small patches), strips, horseshoe or V shaped, and circular mesh or reverse "C" shaped. Many types of materials have been used, mostly polypropylene, PTFE and biologic or absorbable synthetic materials.

Over time, mesh contracts. In circumferential mesh shapes this can cause dysphagia or even erosion into the esophagus. Because of these risks, circular meshes should be avoided at all times.

Mesh erosion into the esophagus is the most feared complication after using mesh. This may result from contraction in circular meshes, but usually results from friction over the edge of a mesh that is not covered by diaphragmatic muscle. Mesh should therefore never be used to bridge a gap in the hiatus. The sole role for mesh is to support and strengthen a hiatal repair. In case of high tension on the repair, left or right collateral diaphragmatic incisions need to be made instead of bridging a gap with artificial material. A lateral incision can be covered with an asymmetric mesh with V shape to cover both hiatal repair and diaphragm incision.

Mesh erosion may initially be suspected due to the development of dysphagia. Usually the area is scarred, and low-grade infection is limited to the direct location of the mesh.

Parts of the mesh can occasionally be removed by endoscopic techniques. Mesh removal by laparoscopy or laparotomy is very difficult and will always result in an esophageal defect that needs to be closed. Oftentimes the damage is tremendous and partial esophageal resection is required. Mesh erosion with limited symptoms should perhaps be accepted without intervention in a clinically stable patient.

As previously described in the paragraph on intraoperative complications, vagal nerve injury is a known complication of hiatal hernia surgery and anti-reflux surgery.

The most common symptoms are dyspeptic complaints, delayed gastric emptying with troublesome intake and/or diarrhea. Any of these complaints are often recognized after the repair of huge hernias because of extensive dissection to create enough esophageal length.

The risk of vagal nerve damage is higher in reoperative hernia repair because it is more difficult to recognize the branches in the often very scarred tissue. The majority of symptoms resolve over time. Meanwhile, conservative treatment should include drugs with prokinetic effects; such as erythromycin, cisapride, metoclopramide or domperidon in combination with professional advice on intake. Improvement of symptoms can be expected up to two years after surgery.

In case of persistent and very severe symptoms of gastroparesis, laparoscopic (robot-assisted) pyloromyotomy or pyloroplasty^{25,26} may be considered, but results are moderate. Serious delayed gastric emptying has to be proven before consideration of this intervention.

Persistent pain after hiatal hernia repair and fundoplication is relatively rare and difficult to treat. Most patients complain of shoulder pain immediately after surgery. This referred pain usually subsides after a few days but may persist sometimes in combination with pain in any abdominal compartment. If the anatomic repair is proven to be intact and reflux is absent, this pain is very difficult to treat. Revision of the repair is not advisable and pain medication in combination with paramedical treatment is the approach of choice.

Two sources of pain are worth mentioning. Dysphagia is often reported as abdominal pain; further in-depth questioning allows for easy distinction. The most important characteristic of dysphagia over other abdominal causes of pain is that the pain always occurs shortly after swallowing.

A second cause of abdominal pain is splenic infarction. The literature is lacking in evidence on the incidence of splenic infarction after fundoplication but is estimated at 1%²⁷⁻²⁹.

The probable cause of these infarctions is ligation of the short gastric vessels during the creation of a fundoplication. The short gastric vessels are responsible for part of the arterial blood supply of the superior pole of the spleen. Generally speaking, the splenic artery will soon take over the blood supply and symptoms subside, however in some cases the ischemia leads to a splenic abscess with possible chronic pain.

CONCLUSION

As with all surgical procedures, adverse events can and will occur. The surgeon should be vigilant to identify these during and after the operation. Those specific to the hiatal hernia repair are discussed above and will aid the surgeon to identify and treat these potential problems.

REFERENCES

1. Joris JL, Chiche JD, Lamy ML. Pneumothorax during laparoscopic fundoplication: diagnosis and treatment with positive end-expiratory pressure. *Anesth Analg*. 1995;81:993–100.
2. Farlo J, Thawgathurai D, Mikhail M, et al. Cardiac tamponade during laparoscopic Nissen fundoplication. *Eur J Anaesthesiol*. 1998;15:246–7.
3. Swide CE, Nyberg PF. Cardiac trauma: an unusual cause of dysrhythmias and electrocardiographic changes during laparoscopic Nissen fundoplication. *Anesthesiology*. 1996;85:209–11.
4. Kempainen E, Kiviluoto TEK. Fatal cardiac tamponade after emergency tension-free repair of a large paraesophageal hernia. *Surg Endosc*. 2000;14:593.
5. Watson I, de Beaux AC. Surgical endoscopy complications of laparoscopic antireflux surgery. *Surg Endosc*. 2001;15:131.
6. Lindeboom MYA, Ringers J, van Rijn PJJ, et al. Gastric emptying and vagus nerve function after laparoscopic partial fundoplication. *Ann Surg*. 2004;240:785–90.
7. Low DE, Mercer CD, James EC, Hill LD. Post Nissen syndrome. *Surg Gynecol Obstet*. 1988;167:1–5.
8. Mertens AC, Tolboom RC, Zavrtnik H, et al. Morbidity and mortality in complex robot-assisted hiatal hernia surgery: 7-year experience in a high-volume center. *Surg Endosc*. 2018;1:3.
9. Zhang C, Liu D, Li F, et al. Systematic review and meta-analysis of laparoscopic mesh versus suture repair of hiatus hernia: objective and subjective outcomes. *Surg Endosc*. 2017;31:4913–22.
10. Gehrig T, Mehrabi A, Fischer L, et al. Robotic-assisted paraesophageal hernia repair—a case-control study. *Langenbeck's Arch Surg*. 2013;398:691–6.
11. Tolboom R, Broeders I, Draaisma W. Robot-assisted laparoscopic hiatal hernia and antireflux surgery. *J Surg Oncol*. 2015;112:266–70.
12. Brenkman HJF, Parry K, Van Hillegersberg R, Ruurda JP. Robot-assisted laparoscopic hiatal hernia repair: promising anatomical and functional results. *J Laparoendosc Adv Surg Tech A*. 2016;26(6):465–9.
13. Müller-Stich BP, Reiter MA, Mehrabi A, et al. No relevant difference in quality of life and functional outcome at 12 months' follow-up—a randomised controlled trial comparing robot-assisted versus conventional laparoscopic Nissen fundoplication. *Langenbeck's Arch Surg*. 2009;394:441–6.
14. Broeders JAJL, Mauritz FA, Ahmed Ali U, et al. Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. *Br J Surg*. 2010;97:1318–30.
15. Du X, Wu J-M, Hu Z-W, et al. Laparoscopic Nissen (total) versus anterior 180° fundoplication for gastro-esophageal reflux disease: a meta-analysis and systematic review. *Medicine (Baltimore)*. 2017;96:e8085.
16. Roks DJ, Broeders JA, Baigrie RJ. Long-term symptom control of gastro-oesophageal reflux disease 12 years after laparoscopic Nissen or 180° anterior partial fundoplication in a randomized clinical trial. *Br J Surg*. 2017;104:852–6.

17. Broeders JA, Roks DJ, Ahmed Ali U, et al. Laparoscopic anterior 180-degree versus nissen fundoplication for gastroesophageal reflux disease: systematic review and meta-analysis of randomized clinical trials. *Ann Surg.* 2013;257:850–9.
18. Oelschläger BK, Pellegrini CA, Hunter JG, et al. Biologic prosthesis to prevent recurrence after laparoscopic paraesophageal hernia repair: long-term follow-up from a multicenter, prospective, randomized trial. *ACS.* 2011;213:461–8.
19. Granderath FA, Schweiger UM, Kamolz T, et al. Laparoscopic Nissen fundoplication with prosthetic hiatal closure reduces postoperative intrathoracic wrap herniation: preliminary results of a prospective randomized functional and clinical study. *Arch Surg.* 2005;140:40–8.
20. Furnée EJB, Draaisma WA, Simmermacher RK, et al. Long-term symptomatic outcome and radiologic assessment of laparoscopic hiatal hernia repair. *Am J Surg.* 2010;199:695–701.
21. Furnée EJB, Draaisma WA, Broeders IAMJ, Gooszen HG. Surgical reintervention after failed antireflux surgery: a systematic review of the literature. *J Gastrointest Surg.* 2009;13:1539–49.
22. Gee DW, Andreoli MT, Rattner DW. Measuring the effectiveness of laparoscopic antireflux surgery. *Arch Surg.* 2008;143:482.
23. Terry M, Smith CD, Branum GD, et al. Outcomes of laparoscopic fundoplication for gastroesophageal reflux disease and paraesophageal hernia. *Surg Endosc.* 2001;15:691–9.
24. Tam V, Winger DG, Nason KS. A systematic review and meta-analysis of mesh vs suture cruroplasty in laparoscopic large hiatal hernia repair. *Am J Surg.* 2016;211:226–38.
25. Toro JP, Lytle NW, Patel AD, et al. Efficacy of laparoscopic pyloroplasty for the treatment of gastroparesis. *J Am Coll Surg.* 2014;218:652–60.
26. Shada AL, Dunst CM, Pescarus R, et al. Laparoscopic pyloroplasty is a safe and effective first-line surgical therapy for refractory gastroparesis. *Surg Endosc.* 2016;30:1326–32.
27. Wilkinson NW, Edwards K, Adams ED. Splenic infarction following laparoscopic nissen fundoplication: management strategies. *JLS.* 2003;7(4):359–65.
28. Ipek T, Eyuboglu E, Ozben V. Partial splenic infarction as a complication of laparoscopic floppy Nissen fundoplication. *J Laparoendosc Adv Surg Tech A.* 2010;20:333–7.
29. Martínez DG, Sánchez AW, García AP. Splenic abscess after laparoscopic Nissen fundoplication: a consequence of short gastric vessel division. *Surg Laparosc Endosc Percutan Tech.* 2008;18:82–5.

CHAPTER THREE

Redo Hiatal Hernia Surgery:
Robotic Laparoscopic Approach

AC Mertens, IAMJ Broeders

Robotic Surgery Second edition, 2021



INTRODUCTION

In the first decades of hiatal hernia repair, surgical outcomes were unsatisfactory and patients were generally counseled to refrain from searching surgical repair. This was especially true for reoperations. Given the increasing success rates, low morbidity, and low mortality seen in recent publications, surgical treatment is becoming more accepted. This is welcome, given the perspective that recurrence of hiatal hernias is seen in up to 40% of patients and redo surgery is indicated in some 10%¹⁻⁴. It is important to discuss these facts at the time of preoperative counseling, as recurrence is the major cause of dissatisfaction after surgery for reflux disease or hiatal hernia. Publications showing high recurrence rates often base these rates on radiology findings. However, counseling for redo surgery should not be based on radiologic studies but rather on the symptomatology of the patient, as slipped funduplications may still provide good reflux control without dysphagia^{5,6}. Symptoms of a recurrent hiatal hernia vary greatly, and it is of the utmost importance to differentiate between a symptomatic recurrent hernia and, for example, abdominal complaints caused by delayed gastric emptying due to vagal nerve damage. The latter will not benefit from a redo hiatal hernia repair, as the symptoms of vagal nerve damage leading to the consultation will not be treated.

DIAGNOSTIC TOOLS: WHEN TO CONSIDER SURGICAL REPAIR

Due to the large number of patients with an asymptomatic recurrence, it is of great importance to ascertain the relation between the recurrent hiatal hernia and the patients' symptoms. Each presentation requires a tailored approach. As is often the case in medicine, the first step in the diagnostic process is taking a detailed medical history. If the symptoms match with the profile of a recurrent hernia, one should proceed to obtaining imaging studies. A plain CT scan of the thorax and upper abdomen combined with exclusively oral contrast is an easy, fast, and affordable method to acquire the required anatomical information. This type of imaging allows for an optimal visualization of all types of (recurrent) hernias and can be used in the workup of all patients considering surgical treatment of a (recurrent) hernia or antireflux surgery. When in doubt, an esophageal barium swallow X-ray series may reveal additional detailed information, especially in the case of dysphagia. Upper gastrointestinal endoscopy may be of value to show a limited shift of the gastroesophageal junction and rule out esophagitis, Barrett's metaplasia, or malignant disorders. If no evidence of a recurrent hernia is found, the next step depends on the patient history. If the main complaint is reflux, high-resolution manometry combined with 24-hour pH measurement is required to objectively diagnose esophageal reflux as the cause of the symptomatology. Gastric emptying studies can be of value in case of serious dyspeptic symptoms if no anatomical

substrate for the symptoms can be found. After objectively confirming delayed gastric emptying, both surgical and conservative treatments can be considered. The treatment of delayed gastric emptying, however, is outside of the scope of this chapter. If a CT scan does indicate wrap disruption, migration, or a newly developed paraesophageal hernia, these anatomic recurrences can be classified using the Hinder classification. Surgical therapy can be indicated when the symptomatology outweighs the risks of surgery^{7,8}.

CATEGORIZING FAILED REPAIRS

Most failed repairs are diagnosed within 5 years of primary surgery^{9,10}. Immediate failure is usually diagnosed by persistent dysphagia, although partial or complete recurrent herniation can be seen within the days or weeks after surgery. These early recurrences may be caused by excessive strain on the crus, caused by physical activity, coughing, or vomiting, often combined with a frail diaphragm. Technical failures may also lead to early recurrent herniation. Some of these early failures can be caused by incomplete hernia sac resection, inadequate esophageal mobilization, suturing under excessive tension, or inadequate hiatal closure. When an early recurrence is diagnosed, minimally invasive repair should be attempted as soon as possible. A delay can give the body opportunity to form dense adhesions, impeding gastric and esophageal mobilization from the thoracic cavity. This in turn increases chances for conversion to open surgery and the risk of serious morbidity. Early dysphagia is a common symptom after surgery, and spontaneous resolution can be awaited when a diet of fluids is enough to provide sufficient nutrients and fluids.

Complete or near-complete esophageal or gastric blockage of fluids requires further investigation. An esophageal barium swallow X-ray series or CT scan with oral contrast may reveal the cause, but upper gastrointestinal endoscopy is usually indicated to exclude fungal infection or blockage by solid food. The endoscopy can be combined with therapeutic balloon dilatation and/or placement of a feeding catheter when required. In severe cases, a multi-lumen tube can be inserted to allow gastric drainage while, at the same time, delivering sustenance distal from the pylorus. If no improvement in dysphagia is seen in the first 3 months and dilatation does not help, surgical intervention can be considered. The preoperative workup should include imaging to exclude or diagnose any recurrent herniation, combined with an upper gastrointestinal endoscopy to ascertain the condition of the esophageal mucosa. Persistent early dysphagia without recurrence of a hiatal hernia is often caused by an overly tight hiatal closure. Other examples of causes for early dysphagia include technical failures in 360-degree funduplications and severe motility disorders of the esophagus.

In case of a prior anterior fundoplication, treatment consists of breakdown of the fundoplication, if it is still (partly) intact. This is then followed by widening the hiatus anteriorly to the esophagus by cutdown of one or more sutures or incision of the hiatal rim until a clear passage into the mediastinum is seen. Following this, a fundoplication can be recreated. In case of a 360° fundoplication, the Nissen sutures are cut, the hiatus is widened as described, and the fundoplication is restored in a 270° fashion. Dissection has to be performed with great caution to avoid damage of the anterior trunk of the vagal nerve as much as possible.

Early redo surgery for recurrence or persistent dysphagia is relatively uncommon and usually entails less than 2% of surgical cases. The majority of redo surgery is performed for recurrence of hiatal hernias or failed reflux control of the fundoplication. Redo surgery is performed in up to 10% of all initial procedures. This percentage is even higher in type 3 and 4 hiatal hernias. The majority of revisions are performed in the first 5 years after the initial procedure. The types of failed fundoplications have been classified by Hinder, based on radiologic findings on barium swallow studies or CT scans. Hinder distinguished four types of failed fundoplication⁸. In Hinder type 1, a complete or almost complete disruption of the fundoplication wrap is seen, usually with recurrence of the hiatal hernia. This may be caused by insufficient thoracic esophageal dissection and incomplete hernia sac dissection. Any suture from stomach to esophagus may fail in time due to persistent traction, and sutures including the hiatal rim will fail in the end when upward forces due to tension on the esophagus persist. Hinder type 2 failure regards slippage of part of the stomach above the diaphragm, often caused by placing the fundoplication around the upper stomach instead of the esophagus.

Hinder type 2 recurrence is usually seen after repair of type 3 and 4 hiatal hernias. In Hinder type 3 failure, one sees slippage of the stomach through a fundoplication while the gastroesophageal junction is still at, or below, the level of the hiatus. This type of failure usually relates to technical failures when creating a 360° Nissen fundoplication. Slippage through a 360 fundoplication might indicate insufficient esophageal dissection or lengthening. In Hinder type 4 failure, the complete and intact wrap has moved upward into the chest, usually just above the diaphragm. This type of failure is encountered frequently after surgery for reflux or type 1 hiatal hernias, certainly when performing radiologic investigation at long term. Wrap migration as seen on radiologic investigation is certainly no reason for intervention by itself, because many patients still encounter good reflux control without dysphagia^{5,6}. Other failed repairs may be caused by crural disruption or adhesions.

INDICATIONS FOR REDO SURGERY

Patients usually encounter a gradual return of symptoms over a period of months or years. Some patients will report a sudden episode of severe pain or the sensation of a snap, with immediate recurrence of symptoms. When recurrence has been diagnosed as described earlier in this chapter, counselling the patient is the next step. The choice between redo surgery, on the one hand, and no intervention supported by medication and dietary advice, on the other hand, should be based on severity of symptoms and the risk profile of redo surgery. In general, redo surgery has a lower satisfaction rate of about 70% and a higher percentage of perioperative morbidity and mortality¹¹⁻¹³. When symptoms are mild or well controlled by medication, one should defer intervention due to the surgical risks and a suboptimal expected outcome.

It is important to mention the increased risk of vagal nerve damage in redo surgical interventions, especially to branches of the anterior vagal trunk. These branches are often embedded in the scar tissue at the upper hiatal rim and can be very difficult to identify. Damage may result in severe and lasting dyspeptic complaints. At this point in time, recurrence of hiatal hernias is unavoidable even for the most experienced surgeons. It should not be regarded as personal failure, and such feelings should not play any role in the decision to proceed to repair. When the decision is made to proceed with redo surgery, the surgeon has the choice between an abdominal and transthoracic approach through either open or endoscopic surgery.

Endoscopic surgery has definite advantages over open surgery due to the reduced tissue damage but may be very challenging due to dense adhesions and altered anatomy. Robotic assistance can be of explicit value in these less common and more complex cases of recurrent hiatal hernias. For gastrointestinal surgeons, the abdominal laparoscopic route to redo surgery is a well-known approach. Open surgery should be reserved for patients with excessive adhesions. Evidence of these adhesions can usually be found in earlier operating reports and often predict increased difficulty in redo surgery.

The thoracic approach can be regarded as an alternative, when the previous report demonstrates that the abdominal route is no longer feasible. Arguments advocating for a thoracic approach include extensive earlier damage to the esophagus or stomach during dissection or dense adhesions of the esophagus or stomach to the thoracic aorta. A thoracic approach is less commonly performed, and there is limited modern literature on the outcomes in redo hiatal hernia surgery by this approach. It may be a viable alternative in those patients where abdominal access is no longer deemed possible or has a very unattractive risk profile. The technique for the transthoracic approach with robotic assistance is published in Chap. 52.

ROBOTIC APPROACH TO REDO HIATAL HERNIA SURGERY

Due to the fact that redo surgery is not often performed by the surgeon responsible for the primary repair, one of the most important steps in the preparation for surgery is studying prior operating reports. Planning ahead for what to expect during surgery can prevent attempts to gain access through infeasible routes or major surgical complications. Previous surgery outside of the upper abdomen rarely leads to intraoperative difficulties in hiatal repair. Upper abdominal surgery such as an open cholecystectomy, however, may induce adhesions in the area of envisioned trocar placement and should be planned for accordingly.

A Veress needle approach at Palmer's point or an open approach is advised, placing the first trocar in the left upper abdomen to perform adhesiolysis prior to safely placing the remaining trocars. Adhesions after previous open gastric or hiatal hernia surgery may be severe, with the omentum and transverse colon adhering to the upper abdominal wall and liver. A careful open introduction in the left flank is advised in these cases, after which laparoscopic adhesiolysis can be performed. Care should be taken not to perforate the omentum, leading to a view on the lower border of the colon transversum.

For dissection, scissors and bipolar energy devices are the preferred tools, with as little heat production as possible, in order to avoid late perforation of the colon or small bowel. Once the route from the upper abdomen to mid-stomach is cleared, one may progress to docking of the robotic system and subsequently continue the procedure with the robotic system. The operating room setup for redo surgery is equal to the setup for primary surgery. The surgical principles are similar to the primary repair, with modifications made to accommodate for the previously constructed fundoplication and accompanying scar tissue. We advise placing a nasogastric tube prior to surgery in all patients. This serves multiple purposes: besides avoiding aspiration of gastric contents during anesthesia, it enables decompression of the stomach, making manipulation of the stomach during surgery significantly easier. We remove the tube before suturing of the fundoplications, but positioning of a large-bore tube can be an option, based on the surgeon's personal experience and preference.

Trocar placement is performed over a slender "smiling" line with the camera trocar some 5 cm (approximately 2 inches) above the umbilicus, followed by two trocars in a symmetrical fashion on either side (Figure 1). The position of the assistant trocar can be in between camera and flank port on the patient left side or in the left flank. The legs of the patient may be spread with the assistant positioned between them, or they can be positioned in a straight line with the assistant on the patient's

left side. It is advisable to experiment with these two setups to find the preferred scenario (Figure 2). The positioning depends on the position of the assistant trocar and the dominant hand of the assistant. The patient is positioned on a mattress that blocks slippage, allowing for steep anti-Trendelenburg or a beach chair table position. The liver retractor is then placed in the flank port on the patient's right side. We use a blunt da Vinci instrument for this purpose, for example, a curved tip grasper. This allows step-by-step retraction of the liver toward the hiatus (Figure 3). A fixed liver retractor can be used, as long as the fixator is low and positioned on the chest. When using such a retractor, one should be certain that collision with robotic arms is avoided.

The fourth arm can then be left unused or applied as an extra retractor through a sixth trocar. The first step in redo surgery is to perform adhesiolysis of the omentum, sac remnants, and stomach from the liver and diaphragm. Blood loss should be avoided in this phase because it will severely hamper insight in the complex anatomy. Robotic dissection strongly supports step-by-step bloodless dissection. It is achievable in

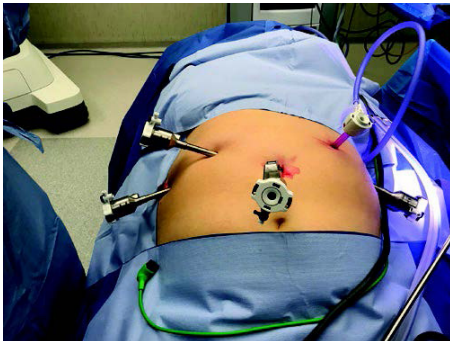


Figure 1 - Trocar positioning for robotic redo hiatal hernia surgery



Figure 2 - Docked XI system for robotic redo hiatal hernia surgery

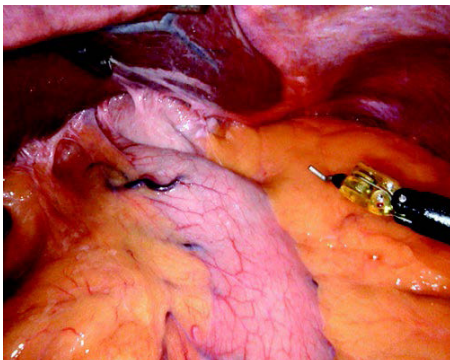


Figure 3 - Curved tip grasper as a dynamic liver retractor

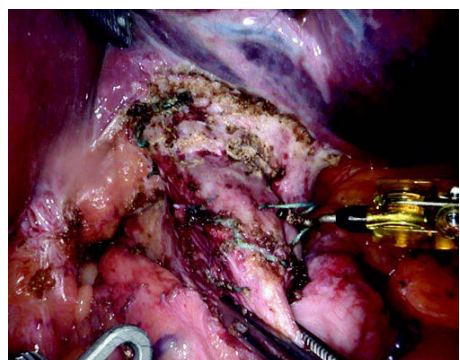


Figure 4 - Takedown of an anterior fundoplication in a patient with retro-esophageal gastric herniation

most cases, and conversion to open surgery can generally be avoided with the use of a robotic system. We experienced a dramatic fall in conversion rates using robotics in redo hiatal hernia surgery^{13,14}. One should, however, be aware of the risk of serious bleeding. The most common cause for this is bleeding from an aberrant left liver lobe artery, which was spared during the primary repair. The presence of such arteries can often be found in prior operating reports. The left gastric artery can sometimes be found in unexpected locations, and the inferior caval vein may be much closer to the hiatus than expected due to retraction caused by scarring from the initial repair. Any aberrant left liver lobe arteries usually have to be ligated to allow proper visualization. One should preferably use clips or a sealing device.

The difficulty of the dissection of the stomach and esophagus from the hiatal rim can vary from easy to difficult (Figure 4). Dissection can be very challenging due to the formation of scar tissue, especially when artificial material has been used at the primary repair or when the first surgery was performed through a laparotomy. There is a definite risk of perforation of the stomach or fundoplication in this phase. Serosal tears of the stomach surface or superficial muscular tissue do not warrant repair. Gastric perforations, however, should be closed immediately to avoid spillage or further tearing of the defect. Closure of the defect can be performed with standard absorbable sutures, but a barbed suture wire makes the task easier and faster. It is advisable to inspect the repair at the end of the procedure to make sure no dehiscence occurred due to the manipulation during the remainder of the procedure. Removing any sutures from the prior fundoplication can lead to microscopic perforations, and this area should be covered by the new fundoplication or diaphragm to protect the vulnerable tissue.

Antibiotic treatment other than the regular perioperative prophylaxis is not required. If repetitive gastric perforations occur without true progression in the procedure, this should be interpreted as a sign to abort the procedure and seek other treatment modalities. Gastric perforations that are closed properly seldom give rise to postoperative problems. The opposite is true for esophageal perforations, which are difficult to close due to vulnerability of the tissue and low healing capacity. Direct repair is warranted, and the repaired area should be covered by a fundoplication at all times. A contrast swallow X-ray or CT scan should be performed at the slightest suspicion of leakage because any delay will lead to fulminant mediastinitis with serious consequences. Postoperative leakage can be treated by esophageal stenting in combination with mediastinal drainage. The latter can be performed through a percutaneous approach, thoracoscopy, thoracotomy, or sometimes by a laparoscopic transhiatal approach.

Hernia sac dissection can be very difficult in redo surgery, especially when the hernia sac dissection was not completely dissected during the primary procedure. Adhesions to the pleura and aorta may be very dense. Remnants of the hernia sac may be left in the mediastinum, as long as adequate mobilization of the esophagus is performed and the hiatal rims are cleared of the peritoneal sac. Dissection at the gastroesophageal junction should be performed with great care because patients are much more prone to vagal nerve damage in redo surgery. The main vagal trunks may be difficult to recognize in the scar tissue, and they may be positioned further away from the esophageal tube than usual. The reported incidence of accidental vagal nerve injury in primary hiatal hernia repair in the available literature is around 2%, although publications primarily describe the incidence in open surgery¹⁵⁻¹⁸. We suspect the incidence in redo surgery is significantly higher. Vagal nerve injury can lead to delayed gastric emptying, which is one of the feared complications of hiatal hernia repair.

The pleura is often damaged in redo surgery, even though damage to the actual pulmonary parenchyma hardly ever occurs. If pleural defects occur, it is generally sufficient for the anesthesiologist to raise the end expiratory pressure to 15 mmHg and lower the abdominal pressure to 10 mmHg. Closure of the defect is seldom necessary, but careful release of residual CO₂ is advised at the end of the procedure, using suction if needed. There is no need for routine thoracic drainage, although a chest X-ray should be performed at the recovery to rule out any significant pneumothorax. Drainage with a small-bore percutaneous drain can be performed in the case of pulmonary collapse, but this is encountered very rarely when taking measures as described.

Besides damage to the pulmonary tissue, adhesions to vascular structures in the mediastinum can greatly complicate the procedure. Especially when little is known about the primary repair, one should pay close attention to the location of the aorta, vena cava, and aorto-esophageal branches. These structures can become encased in scar tissue, and careful step-by-step dissection is needed. Accidental damage to these structures can quickly limit the visibility of the surgical field. The visualization and dissection capacities of the robotic system provide support in this phase.

After the intra-thoracic contents of the hernia sac have been removed from the mediastinum and a tension-free position of the esophagus has been achieved, hiatal closure is performed. We advise using interrupted, nonabsorbable braided 2-0 sutures for this. Sutures are placed both anteriorly and posteriorly of the esophagus in order to spread the tension on the hiatus and to avoid kinking of the esophagus at the level of the hiatal opening.

Mesh can be used at the surgeon's discretion. We have moved from a V-shaped mesh to polypropylene pledgets and use these only when the patient has a frail diaphragm (Figure 5).

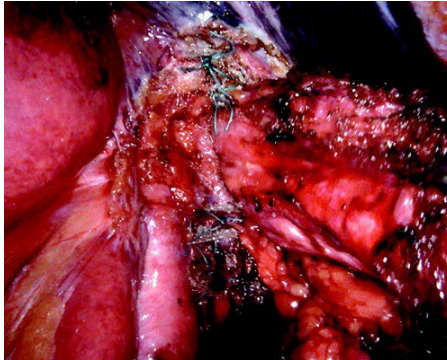


Figure 5 - Frail diaphragm with pledgets

Since evidence for the long-term efficacy of mesh¹⁹ is lacking, we tend to use less mesh, currently in under 10% of redo cases¹³. In rare cases, the crus cannot be approximated with sutures due to frailness or excessive tension with the risk of tearing. In these cases, a lateral diaphragmatic incision can be made to relieve some of this tension. The incision can be made the left or right side, depending on the circumstances. After hiatal closure, both the hiatal crura and the defect are covered with mesh. The mesh is preferably secured by sutures, although tackers may be used in the lower part, taking care not to use these near the cardiac protrusion in order to prevent damage to the pericardium. Suturing with barbed running sutures is the easiest way to secure mesh over long distances.

The choice of the type of fundoplication differs on a patient-to-patient basis. In the case of large hiatal hernias, we prefer an anterior partial fundoplication in order to mimic the normal anatomy as much as possible. In patients who predominantly suffer from reflux, with normal anatomy or a type 1 hiatal hernia at the initial procedure, we create a posterior partial 270-degree fundoplication. The 360-degree fundoplication should be reserved for severe reflux when other types of fundoplications have failed. There is no evidence for long-term superiority of 360-degree fundoplications, while the incidence of comorbidity is significantly higher, especially bloating and dysphagia²⁰⁻²⁴.

SUMMARY/CONCLUSION

Redo hiatal hernia surgery can be challenging, especially after prior upper abdominal laparotomy or the use of artificial material at the initial hiatal repair. Robotic assistance greatly provides support in the careful dissection of the hiatus and during hiatal repair. The use of robotics has proven to lower conversion rates. Principles and technical approaches are described in this chapter.

REFERENCES

1. Oelschlagel BK, Pellegrini CA, Hunter J, Soper N, Brunt M, Sheppard B, et al. Biologic prosthesis reduces recurrence after laparoscopic paraesophageal hernia repair. *Trans Meet Am Surg Assoc.* 2006;124:146–55.
2. Sathasivam R, Bussa G, Viswanath Y, Obuobi R-B, Gill T, Reddy A, et al. ‘Mesh hiatal hernioplasty’ versus ‘suture cruroplasty’ in laparoscopic para-oesophageal hernia surgery; a systematic review and meta-analysis. *Asian J Surg.* 2019;42(1):53–60.
3. Asti E, Lovece A, Bonavina L, Milito P, Sironi A, Bonitta G, et al. Laparoscopic management of large hiatus hernia: five-year cohort study and comparison of mesh-augmented versus standard crura repair. *Surg Endosc.* 2016;30(12):5404–9.
4. Zhang C, Liu D, Li F, Watson DI, Gao X, Koetje JH, et al. Systematic review and meta-analysis of laparoscopic mesh versus suture repair of hiatus hernia: objective and subjective outcomes. *Surg Endosc.* 2017;31(12):4913–22.
5. Dunne N, Stratford J, Jones L, Sohampal J, Robertson R, Booth MI, et al. Anatomical failure following laparoscopic antireflux surgery (LARS): does it really matter? *Ann R Coll Surg Engl.* 2010;92(2):131–5.
6. Donkervoort SC, Bais JE, Rijnhart-de Jong H, Gooszen HG. Impact of anatomical wrap position on the outcome of Nissen fundoplication. *Br J Surg.* 2003;90(7):854–9.
7. Fundoplication F, Kim RH, Gates T, Agostino HRD. Imaging findings of successful. *Radiographics.* 2014;34(7):1873–85.
8. Hinder RA, Klingler PJ, Perdakis G, Smith SL. Management of the failed antireflux operation. *Surg Clin North Am.* 1997;77(5):1083–98.
9. Stefanidis D, Hope WW, Kohn GP, Reardon PR, Richardson WS, Fanelli RD. Guidelines for surgical treatment of gastroesophageal reflux disease. *Surg Endosc.* 2010;24(11):2647–69.
10. Mittal SK, Bikhchandani J, Gurney O, Yano F, Lee T. Outcomes after repair of the intrathoracic stomach: objective follow-up of up to 5 years. *Surg Endosc.* 2011;25(2):556–66.
11. Chen Z, Zhao H, Sun X, Wang Z. Laparoscopic repair of large hiatal hernias: clinical outcomes of 10 years. *ANZ J Surg.* 2018;88(10):E703–7.
12. Zahiri HR, Weltz AS, Sibia US, ParANJI N, Leydorf SD, Fantry GT, et al. Primary versus redo paraesophageal hiatal hernia repair: a comparative analysis of operative and quality of life outcomes. *Surg Endosc.* 2017;31(12):5166–74.
13. Mertens AC, Tolboom RC, Zavrtnik H, Draaisma WA, Broeders IAMJ. Morbidity and mortality in complex robot-assisted hiatal hernia surgery: 7-year experience in a high-volume center. *Surg Endosc.* 2019;33(7):2152–61.
14. Tolboom R, Broeders I, Draaisma W. Robot-assisted laparoscopic hiatal hernia and antireflux surgery. *J Surg Oncol.* 2015;112(3):266–70.
15. Low DE, Mercer CD, James EC, Hill LD. Post Nissen syndrome. *Surg Gynecol Obstet.* 1988;167(1):1–5.
16. Watson DI, de Beaux AC. Complications of laparoscopic antireflux surgery. *Surg Endosc.* 2001;15(4):344–52.

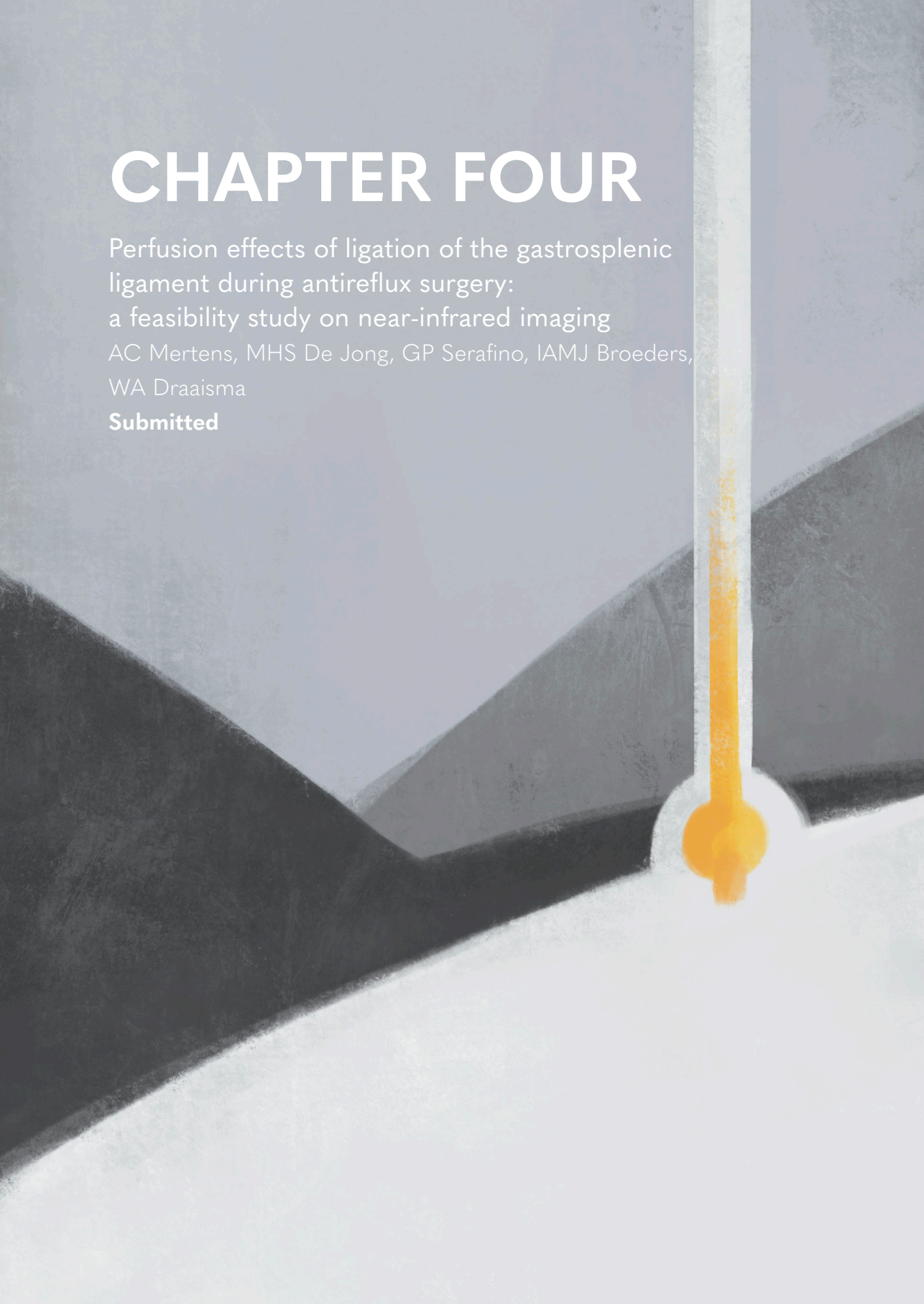
17. Watson I, de Beaux AC. Complications of laparoscopic antireflux surgery. *Surg Endosc.* 2001;15:131.
18. Lindeboom MYA, Ringers J, van Rijn PJJ, Neijenhuis P, Stokkel MPM, Masclee AAM. Gastric emptying and vagus nerve function after laparoscopic partial fundoplication. *Ann Surg.* 2004;240(5):785–90.
19. Tam V, Winger DG, Nason KS. A systematic review and meta-analysis of mesh vs suture cruroplasty in laparoscopic large hiatal hernia repair. *Am J Surg.* 2016;211(1):226–38.
20. Du X, Wu J-M, Hu Z-W, Wang F, Wang Z-G, Zhang C, et al. Laparoscopic Nissen (total) versus anterior 180° fundoplication for gastro-esophageal reflux disease: a meta-analysis and systematic review. *Medicine (Baltimore).* 2017;96(37):e8085.
21. Du X, Hu Z, Yan C, Zhang C, Wang Z, Wu J. A meta-analysis of long follow-up outcomes of laparoscopic Nissen (total) versus Toupet (270°) fundoplication for gastro-esophageal reflux disease based on randomized controlled trials in adults. *BMC Gastroenterol.* 2016;16(1):88.
22. Broeders JAJL, Mauritz FA, Ahmed Ali U, Draaisma WA, Ruurda JP, Gooszen HG, et al. Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. *Br J Surg.* 2010;97(9):1318–30.
23. Roks DJ, Broeders JA, Baigrie RJ. Long-term symptom control of gastro-oesophageal reflux disease 12 years after laparoscopic Nissen or 180° anterior partial fundoplication in a randomized clinical trial. *Br J Surg.* 2017;104(7):852–6.
24. Broeders JA, Roks DJ, Ahmed Ali U, Watson DI, Baigrie RJ, Cao Z, et al. Laparoscopic anterior 180-degree versus nissen fundoplication for gastroesophageal reflux disease: systematic review and meta-analysis of randomized clinical trials. *Ann Surg.* 2013;257(5):850–9.

CHAPTER FOUR

Perfusion effects of ligation of the gastrosplenic ligament during antireflux surgery:
a feasibility study on near-infrared imaging

AC Mertens, MHS De Jong, GP Serafino, IAMJ Broeders,
WA Draaisma

Submitted



ABSTRACT

Aim

Division of the gastrosplenic ligament during antireflux surgery is commonly regarded as necessary to create a tensionfree fundoplication. This ligament contains vascular structures supplying the gastric fundus and spleen and division could lead to ischemia. The true incidence of splenic infarction may be underestimated due to diagnostic reasons.

Methods

This study aimed to examine the feasibility of determining the occurrence and extent of vascularization defects in the spleen and gastric fundus using near-infrared imaging. Ten patients undergoing fundoplication were included. Patients were administered indocyanine green before and after division of the gastrosplenic ligament. During surgery, observers scored the perfusion of the spleen under near-infrared imaging. Intraoperative video clips were scored by a radiologist unfamiliar with the procedure (GS).

Results

Before division of the gastrosplenic ligament, all observers scored 'no defect' for all patients. After division of the gastrosplenic ligament, two patients were scored with 'definite defect' by all observers, including the consulted radiologist (GS).

Conclusion

Assessing the perfusion of the spleen during antireflux surgery is feasible with near-infrared imaging. We suggest further research in a larger cohort of patients undergoing visual near-infrared intraoperative inspection of the spleen before and after ligation of the ligament, combined with patient reported outcomes.

INTRODUCTION

The gastrosplenic ligament connects the greater curvature of the stomach with the hilum of the spleen, and contains the short gastric and left gastro-epiploic vessels. Most surgeons regard the division of the gastrosplenic ligament during antireflux surgery as necessary to create a tension free fundoplication, as ligating the ligament enables additional mobilization of the stomach. The short gastric vessels are part of the blood supply to both the superior pole of the spleen and the gastric fundus, although there is uncertainty regarding the flow direction and anatomical variation. Peripheral splenic arterial branches have little collateral circulation, which means that ligating the short gastric vessels could result in (partial) infarction of the spleen, gastric fundus or both.

While partial infarction of the spleen in patients with chronic pain after antireflux surgery has a reported incidence of around 1%¹⁻³, the true incidence of infarction is unknown. Since a splenic infarction has a large overlap in symptoms with the normal postoperative course of antireflux surgery, we suspect that infarction is underreported. Additionally, it is unclear if and to what extent postoperative pain is associated with the altered vascularization of the spleen or stomach.

Minimally invasive surgery has improved the postoperative recovery period to the point where postoperative pain is among the main barriers for outpatient treatment. If splenic or gastric infarction can be linked to postoperative pain, and preserving the gastrosplenic ligament reduces the incidence of postoperative splenic infarctions and pain, this could be an argument to preserve the gastrosplenic ligament if possible. As the need for ligation of the gastrosplenic ligament remains the subject of debate in recent literature⁴⁻⁹, research in this direction could improve patient outcomes.

Our hypothesis is that many splenic and gastric infarctions occur following the division of the gastrosplenic ligament and structures therein, which might be a source of postoperative pain due to vascularization defects. Since near-infrared imaging is becoming more readily available, this technique gives surgeons the ability to obtain live imaging of vascularization and circulation, allowing immediate feedback on the results of tissue and vessel manipulation¹⁰⁻¹⁵. This study aimed to examine the feasibility of determining the occurrence and extent of vascularization defects in the spleen and gastric fundus using near-infrared imaging.

METHODS

This monocenter prospective observational study was conducted between October 2018 and May 2019 in the Jeroen Bosch Ziekenhuis in 's-Hertogenbosch, the Netherlands, at the department of surgery. This study aimed to examine the feasibility of determining the occurrence and extent of vascularization defects in the spleen and gastric fundus using near-infrared imaging.

This study was approved by both the regional ethical committee (METC Noord-Brabant) and the local ethical committee of the Jeroen Bosch hospital. The study was registered with trialregister.nl under NL66435.028.18, in accordance with national guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975 and later versions.

When a patient was referred to a participating surgeon for antireflux surgery, the surgeon ensured that the indication for surgery is valid through a selection of detailed medical history, physical examination, upper endoscopy results, pH measurements, manometry and CT imaging. After receiving informed consent for surgical treatment, the surgeon discussed inclusion in the study with the patient. The patient then received study information from the researcher and received sufficient time for consideration of participating in the study. Before surgery, the researcher ascertained that the patient was suitable for the trial. This means that the patient met all the inclusion criteria and did not meet any of the exclusion criteria. After informed consent was obtained by the researcher, the patient was enrolled in the study. This pilot study is conducted with a sample size of 10 patients.

INCLUSION AND EXCLUSION CRITERIA

Inclusion in the study was considered for patients 18 years or older with objectively proven gastro-esophageal reflux disease. Patients were excluded if they were pregnant, breastfeeding, had previous gastric/esophageal surgery, achalasia or were unable to provide informed consent. In addition, due to the study procedures including the administration of indocyanine green, patients with known adverse reactions to indocyanine green, sodium iodide or iodide were excluded, as were patients with liver insufficiency or a glomerular filtration rate lower than 40.

OUTCOMES

The primary outcome was the intraoperative observation of the vascularization of the gastric fundus and spleen. The three possible outcomes (no perfusion defect, possible perfusion defect or definite perfusion defect) as reported by the surgeon, assistant and researcher were recorded.

In an attempt to diminish potential bias caused by viewing the entire procedure with knowledge of the patient, an external expert was consulted. After surgery, a radiologist (GS) unfamiliar with the surgical procedure but experienced in judging perfusion in fluoroscopy was shown a recording of the near-infrared imaging. The same scoring system described earlier was used to record the judgement of the radiologist. The footage was cut to prevent the identification of the patient or the phase of the surgery, which means that the radiologist did not know if the clip was recorded before or after ligation of the ligament. To further prevent bias, the video clips were shown in random order. The secondary outcomes were the observation of gastric fundus and spleen vascularization reported by the radiologist after viewing the footage, in addition to the time it took to achieve sufficient perfusion of indocyanine green under near-infrared lighting (time to visualization).

Patient reported outcome measures, such as postoperative pain or quality of life, were not included in the study since the sample size would not be sufficient for meaningful analysis. As the fundoplication was created after the end of data collection during the second measurement, no outcome data were recorded regarding the type of fundoplication.

STUDY PROCEDURE

All procedures were performed on a Da Vinci Xi robotic assisted surgery system equipped with Firefly©. During surgery, two doses of indocyanine green (Verdye©) were administered by the anesthesiologist; once before (measurement one) and once directly after (measurement two) ligation of the gastrosplenic ligament. The second dose was administered at least 15 minutes apart from the first dose to ensure that the ICG was sufficiently cleared from the circulation. The dosage was set at 10mg (5mg/ml, diluted in saline for injection as per the SPC or Summary of Product Characteristics) in a single bolus injection through a peripheral IV, followed by 5ml saline for injection to flush the IV. From the time of injection of the indocyanine green to the moment of adequate assessment of perfusion, the Firefly© system was enabled, and endoscopic video data was recorded for evaluation. Independent observations of the surgeon, assistant and researcher were recorded. After the surgery, the recorded images were assessed by the surgeon, researcher and a radiologist (GS) unfamiliar with the surgical procedure following the same procedures. According to the standard local treatment protocol, patients received a follow-up appointment at the outpatient clinic 6 weeks after surgery. This follow-up appointment was not part of the study protocol.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS version 25. Data recorded was derived from demographic data (ie. age, gender) and observations made intraoperatively. Assessments by the surgeon, assistant, researcher and radiologist were analyzed for inter-observer variability. Binary and categorical data will be presented as a number, accompanied by the percentage of the total. Continuous variables will be presented as either a mean value with standard deviation or median with range and interquartile range, depending on the distribution of the data. Intra- and interobserver variability were assessed using the Intraclass Correlation Coefficient (ICC). An ICC of 0.7 or higher was regarded as adequate.

RESULTS

Between December 2018 and May 2019, all 10 planned inclusions were achieved. All patients eligible for the study met the inclusion criteria, provided informed consent and were subsequently included in the study. All patients underwent a robot-assisted fundoplication as planned.

Baseline characteristics of the included patients are depicted in Table 1. The median age of the included patients was 57 years old, with a median BMI of 28. 40% of the patients was male, with a median ASA score of 2. One patient underwent a prior laparoscopic cholecystectomy, but otherwise no relevant comorbidities were reported.

The protocol described in the methods section was followed correctly in all cases. Table 2a and Table 2b depict the study outcomes. None of the patients showed visual signs of a splenic infarct before injection of indocyanine green. The first measurement, before ligation of the gastrosplenic ligament, did not reveal perfusion defects in any of the 10 patients. All observers reported no defect in all cases. The second measurement, after ligation of the gastrosplenic ligament, showed a definite defect in the superior pole of the spleen in two patients. All observers reported the same score in all cases, both during surgery and when viewing of the recorded video. Screen captures of the perfusion defects are shown in Figure 1 and 2. As all observers reported the same score in all measurements, the Intraclass Correlation Coefficient was 1 in all cases. The gastric fundus did not show evidence of perfusion defects in any of the patients.

TABLE 1. BASELINE CHARACTERISTICS

VARIABLE		
Age (years, median, IQR)		57.5 [49.5-64.0]
Gender (N, %)	Male	4 (40)
	Female	6 (60)
BMI (median, IQR)		28 [25-30]
ASA (median, IQR)		2 [2-2]
Comorbidity (N, %)	Laparoscopic cholecystectomy	1 (10%)
Charlson comorbidity index (median, IQR)		1 [0.75-2.0]
Surgical approach (N, %)	Laparoscopic, robot assisted	10 (100)

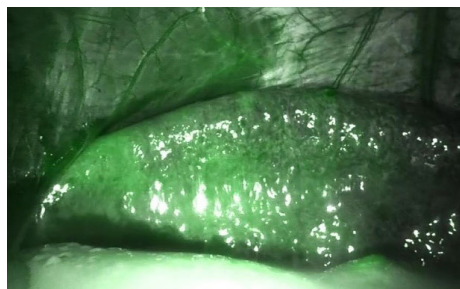


Figure 1a. Patient 6
Before ligation of the gastrosplenic ligament

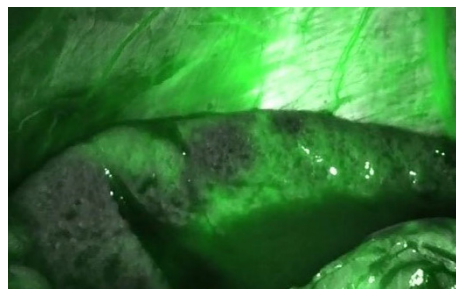


Figure 1b. Patient 6
After ligation of the gastrosplenic ligament

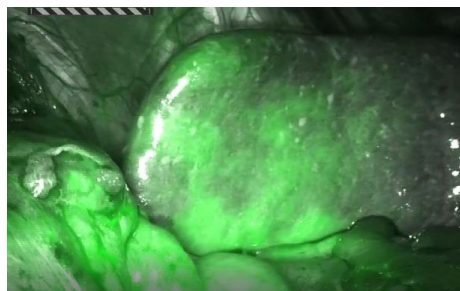


Figure 2a. Patient 9
Before ligation of the gastrosplenic ligament

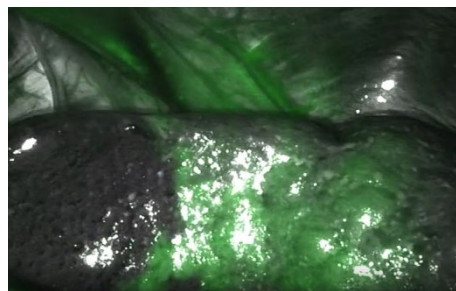


Figure 2a. Patient 9
Before ligation of the gastrosplenic ligament

**TABLE 2A. MEASUREMENT ONE
BEFORE LIGATION OF THE GASTROSPLENIC LIGAMENT**

PATIENT	SURGEON	ASSISTANT	RESEARCHER	VIDEO REVIEW	MAX. ICG SATURATION (SECONDS)
1	No defect	No defect	No defect	No defect	NA
2	No defect	No defect	No defect	No defect	25
3	No defect	No defect	No defect	No defect	20
4	No defect	No defect	No defect	No defect	30
5	No defect	No defect	No defect	No defect	25
6	No defect	No defect	No defect	No defect	60
7	No defect	No defect	No defect	No defect	20
8	No defect	No defect	No defect	No defect	43
9	No defect	No defect	No defect	No defect	35
10	No defect	No defect	No defect	No defect	35

NA: Not available

**TABLE 2B. MEASUREMENT TWO
AFTER LIGATION OF THE GASTROSPLENIC LIGAMENT**

PATIENT	SURGEON	ASSISTANT	RESEARCHER	VIDEO REVIEW	MAX. ICG SATURATION (SECONDS)
1	No defect	No defect	No defect	No defect	40
2	No defect	No defect	No defect	No defect	20
3	No defect	No defect	No defect	No defect	15
4	No defect	No defect	No defect	No defect	30
5	No defect	No defect	No defect	No defect	60
6	Definite defect	Definite defect	Definite defect	Definite defect	20
7	No defect	No defect	No defect	No defect	20
8	No defect	No defect	No defect	No defect	26
9	Definite defect	Definite defect	Definite defect	Definite defect	34
10	No defect	No defect	No defect	No defect	20

DISCUSSION

The aim of this study was to assess the feasibility of determining the incidence of splenic infarction following ligation of the gastrosplenic ligament during fundoplication surgery. We achieved this through utilizing the Firefly© near-infrared imaging capabilities of the Da Vinci Xi robotic assisted surgery system after injecting indocyanine green. None of the patients showed signs of perfusion defects before ligation of the gastrosplenic ligament. Out of 10 included patients, perfusion defects after ligation of the gastrosplenic ligament were seen in two cases, both located in the superior pole of the spleen.

Esophageal reflux is a benign disease with a considerable impact on the quality of life of the patient. Fundoplication surgery is an increasingly safe procedure, and since post-operative pain is still among the main barriers for outpatient treatment, we believe it is essential to evaluate patient reported outcomes such as postoperative pain^{16,17}.

Although part of these symptoms can be explained due to the surgical trauma to the abdominal wall, diaphragm, stomach or esophagus, patients frequently complain of pain in the upper (mainly left upper quadrant) of the abdomen^{1-3,18}. Left upper quadrant abdominal pain coincides with the reported location of perceived pain due to splenic infarction^{3,19}. Many surgeons agree that dividing the gastroesophageal ligament, which contains part of the splenic blood supply, is necessary for creating an adequate floppy fundoplication. The reasoning for this is that ligating the ligament enables additional mobilization of the stomach. However, there is no definitive evidence that this leads to improved outcomes or a higher success rate^{4-9,20}.

While the current literature estimates the incidence of (partial) splenic infarction in patients with chronic pain after antireflux surgery around 1%¹⁻³, authors agree that the true incidence is not known. Since splenic infarctions have a large overlap in symptoms with the normal postoperative course of antireflux surgery¹⁸, we suspect that infarction is vastly underreported. Ipek et al.¹ described splenic infarction in the postoperative course in 20 out of 2100 patients undergoing a laparoscopic floppy Nissen fundoplication, with just 2 patients reporting persistent abdominal pain related to an infarction. All cases were managed conservatively. This seems such a low incidence, that the effort required to diagnose a potential splenic infarction in all patients might not be warranted. As splenic infarctions following antireflux surgery are thought to generally resolve spontaneously, the diagnosis is usually only considered after prolonged symptoms. However, modern surgical techniques have improved postoperative recovery to the point where pain is one of the most important outcomes after antireflux surgery. If postoperative pain after

antireflux surgery is indeed correlated to splenic or gastric infarction, this could be an argument to attempt to preserve the gastrosplenic ligament in antireflux surgery.

Splenic infarction can be diagnosed during surgery, or postoperatively based on symptoms or imaging. In order to determine the chance of a missed diagnosis due to a delay in the discoloration of the spleen due to ischemia during surgery, we considered a study comparing standard laparoscopic observation of the spleen after ligation of the gastrosplenic ligament and near-infrared imaging. This pilot study was performed to determine the feasibility of such a study.

In our small cohort of 10 patients, 2 (20%) showed signs of a splenic infarction during surgery. Although this incidence is considerably higher than the 1% reported in literature, this series is too small to be able to draw conclusions on the incidence in the general population. All of the patients in our cohort were planned for routine fundoplication due to esophageal reflux caused by a small hiatal hernia. None of the patients showed evidence of ischemia in the gastric fundus. Both of the patients with intraoperative infarction had an easily recognizable ischemic demarcation of the spleen with the addition of near-infrared imaging. Outside of the current study, we do not routinely inspect the spleen after division of the gastrosplenic ligament, and therefore would probably not have caught either of these infarctions. This pilot study was designed as a feasibility study, and not for detecting changes in the postoperative course. We do not believe our cohort of 10 patients is sufficiently sized to allow drawing conclusions regarding the incidence, postoperative course and thus the clinical relevance of splenic infarctions.

This study has several limitations. We relied on visual inspection of the perfusion, rather than opting for a quantitative assessment of the indocyanine green presence. We decided upon this method due to the fact that it is not possible to reliably visualize the entire spleen from a single camera position during the entirety of the fundoplication surgery. Between the first and second measurement, the gastrosplenic ligament is ligated and the fundoplication is created. It is not possible to retain the camera position during these actions. All currently available methods that would allow quantitative comparative analysis of near-infrared imaging require a fixed camera position between measurements. However, we are convinced that the perfusion defects found in our cohort would also be identified using a quantitative analysis. It is possible that we missed smaller, or more diffuse, perfusion defects that a quantitative analysis would have classified as decreased perfusion.

Although visualization of the spleen was achieved without difficulty in the majority of cases, we did encounter several issues. In a single case, the time to full visualization of indocyanine green was 60 seconds, we suspected this was caused by pressure of the robotic arm on the splenic artery. After moving the robotic arm, the spleen

displayed adequate perfusion within 2 seconds, revealing adequate perfusion throughout the spleen. This balance between maintaining visibility of the spleen by displacing the other intra-abdominal organs and the obstruction of blood flow provided a small learning curve.

Determining the effects of gastrosplenic ligament ligation using near-infrared imaging is feasible. Two out of the ten included patients in the current study showed signs of a splenic infarct after ligation of the gastrosplenic ligament. This is a significantly higher incidence (20%) than the reported 1% in current literature, however, this cohort is not sufficiently sized to draw any conclusions on the incidence.

CONCLUSION

To determine the true incidence of splenic infarctions after ligation of the gastrosplenic ligament, we suggest further research using a sufficiently sized cohort of patients undergoing visual intraoperative inspection of the spleen using near-infrared, both before and after ligation of the ligament, combined with patient reported outcomes. In addition to this, perfusion should be inspected at the end of the procedure, in order to assess if any ischemia can resolve spontaneously within the span of the procedure. This would enable future studies to report on both the true incidence and the clinical impact of splenic infarctions in this population.

HIGHLIGHT

- Determining the effects of gastrosplenic ligament ligation using near-infrared imaging is feasible.
- Two out of the ten included patients in the current study showed signs of a splenic infarct after ligation of the gastrosplenic ligament. This is a significantly higher incidence (20%) than the reported 1% in current literature.
- Splenic perfusion should be inspected (visually or otherwise) at the end of the procedure.
- Future studies should focus on both the true incidence and the clinical impact of splenic infarctions in this population.

DISCLOSURES

IB reports consulting fees from Johnson & Johnson and Intuitive Surgical, outside the submitted work. AM, MJ, GPS and WD do not have any conflicts of interest or financial ties to disclose.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Ipek T, Eyuboglu E, Ozben V. Partial Splenic Infarction as a Complication of Laparoscopic Floppy Nissen Fundoplication. *J Laparoendosc Adv Surg Tech*. 2010 May;20(4):333–7.
2. Martínez DG, Sánchez AW, García AP. Splenic abscess after laparoscopic Nissen fundoplication: A consequence of short gastric vessel division. *Surg Laparosc Endosc Percutaneous Tech*. 2008 Feb;18(1):82–5.
3. Wilkinson NW, Edwards K, Adams ED. Splenic infarction following laparoscopic Nissen fundoplication: management strategies. *JLS*. 2003;7(4):359–65.
4. Blomqvist a, Dalenbäck J, Hagedorn C, et al. Impact of complete gastric fundus mobilization on outcome after laparoscopic total fundoplication. *J Gastrointest Surg*. 2000;4(5):493–500.
5. O’Boyle CJ, Watson DI, DeBeaux a C, et al. Preoperative prediction of long-term outcome following laparoscopic fundoplication. *ANZ J Surg*. 2002 Jul;72(7):471–5.
6. Watson DI, Pike GK, Baigrie RJ, et al. Prospective double-blind randomized trial of laparoscopic Nissen fundoplication with division and without division of short gastric vessels. *Ann Surg*. 1997;226(5):642–52.
7. Khatri K, Sajid MS, Brodrick R, et al. Laparoscopic Nissen fundoplication with or without short gastric vessel division: A meta-analysis. *Surg Endosc Other Interv Tech*. 2012;26(4):970–8.
8. Luostarinen ME, Isolaari JO. Randomized trial to study the effect of fundic mobilization on long-term results of Nissen fundoplication. *Br J Surg*. 1999;86(5):614–8.
9. Kosek V, Wykypiel H, Weiss H, et al. Division of the short gastric vessels during laparoscopic Nissen fundoplication: Clinical and functional outcome during long-term follow-up in a prospectively randomized trial. *Surg Endosc Other Interv Tech*. 2009;23(10):2208–13.
10. Alander JT, Kaartinen I, Laakso A, et al. A Review of indocyanine green fluorescent imaging in surgery. *Int J Biomed Imaging*. 2012;2012.
11. Sarkaria IS, Bains MS, Finley DJ, et al. Intraoperative Near-Infrared Fluorescence Imaging as an Adjunct to Robotic-Assisted Minimally Invasive Esophagectomy. *Innov Technol Tech Cardiothorac Vasc Surg*. 2014 Feb 3;9(5):391–3.
12. Boni L, David G, Mangano A, et al. Clinical applications of indocyanine green (ICG) enhanced fluorescence in laparoscopic surgery. *Surg Endosc Other Interv Tech*. 2015;29(7):2046–55.
13. Griffiths M, Chae MP, Rozen WM. Indocyanine green-based fluorescent angiography in breast reconstruction. *Gland Surg*. 2016 Apr 1;5(2):133–49.
14. Slooter MD, Eshuis WJ, Cuesta MA, et al. Fluorescent imaging using indocyanine green during esophagectomy to prevent surgical morbidity: A systematic review and meta-analysis. *J Thorac Dis*. 2019;11(Suppl 5):S755–65.
15. van Manen L, Handgraaf HJM, Diana M, et al. A practical guide for the use of indocyanine green and methylene blue in fluorescence-guided abdominal surgery. Vol. 118, *Journal of Surgical Oncology*. John Wiley and Sons Inc.; 2018. p. 283–300.
16. Stefanidis D, Hope WW, Kohn GP, et al. Guidelines for surgical treatment of gastroesophageal reflux disease. *Surg Endosc*. 2010 Nov 20;24(11):2647–69.
17. Kohn K, Price P, Demeester D, et al. SAGES Guidelines for the management of hiatal hernia. *Surg Endosc Interv Tech*. 2013;27(12):4409–28.

18. Bunting DM, Szczebiot L, Peyser PM. Pain after laparoscopic antireflux surgery. *Ann R Coll Surg Engl.* 2014;96(2):95–100.
19. Odabasi M, Abuoglu HH, Arslan C, et al. Asymptomatic Partial Splenic Infarction In Laparoscopic Floppy Nissen Fundoplication And Brief Literature Review. *Int Surg.* 2014;99(3):291–4.
20. Broeders JAJL, Mauritz FA, Ahmed Ali U, et al. Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. *Br J Surg.* 2010 Sep 16;97(9):1318–30.

CHAPTER FIVE

Morbidity and mortality in complex
robot-assisted hiatal hernia surgery:
7-year experience in a high-volume center

AC Mertens, RC Tolboom, H Zavrtanik,
WA Draaisma, IAMJ Broeders

Surgical Endoscopy 2018



ABSTRACT

Introduction

Published data regarding robot-assisted hiatal hernia repair are mainly limited to small cohorts. This study aimed to provide information on the morbidity and mortality of robot-assisted complex hiatal hernia repair and redo anti-reflux surgery in a high-volume center.

Materials and methods

All patients that underwent robot-assisted hiatal hernia repair, redo hiatal hernia repair and anti-reflux surgery between 2011-2017 at the Meander Medical Centre, Amersfoort, the Netherlands were evaluated. Primary endpoints were 30-day morbidity and mortality. Major complications were defined as Clavien-Dindo \geq IIIb.

Results

Primary surgery

211 primary surgeries were performed by two surgeons. The median age was 67 (IQR 58-73) years. 84.4% of patients had a type III or IV hernia (10.9% Type I; 1.4% Type II; 45.5% Type III; 38.9% Type IV, 1.4% no herniation). In 3.3% of procedures conversion was required. 17.1% of patients experienced complications. The incidence of major complications was 5.2%. Ten patients (4.7%) were readmitted within 30 days. Symptomatic early recurrence occurred in two patients (0.9%). The 30-day mortality was 0.9%.

Redo surgery

151 redo procedures were performed by two surgeons. The median age was 60 (IQR 51-68) years. In 2.0% the procedure was converted. The overall incidence of complications was 10.6%, while the incidence of major complications was 2.6%. Three patients (2.0%) were readmitted within 30 days. One patient (0.7%) experienced symptomatic early recurrence. No patients died in the 30-day postoperative period.

Conclusions

This study provides valuable information on robot-assisted laparoscopic repair of primary or recurrent hiatal hernia and anti-reflux surgery for both patient and surgeon. Serious morbidity of 5.2% in primary surgery and 2.6% in redo surgery, in this large series with a high surgeon caseload, has to be outweighed by the gain in quality of life or relief of serious medical implications of hiatal hernia when counseling for surgical intervention.

INTRODUCTION

Minimally invasive surgery is the preferred approach for hiatal hernia repair and anti-reflux procedures with reported success rates of up to 90% in specialized centers¹⁻³. While conventional laparoscopy has gained rapid acceptance over open surgery as the golden standard, this approach is known to be technically demanding. Robotic systems were designed to overcome part of the technical limitations of conventional laparoscopy⁴⁻⁶.

Several previous studies have demonstrated the safety and feasibility of robot-assisted approach in hiatal hernia repair and anti-reflux surgery⁷⁻¹¹, including a paper on the early results from our center comparing conventional laparoscopy to robotic assisted surgery⁹. The majority of current publications focus on more common anti-reflux procedures in the absence of hiatal herniation or type 1 hiatal hernia. In contrast, publications on relatively rare complex hiatal hernia repairs remain limited to a few single-center, low-volume case series and a few small comparative studies^{7-9,12,13}. As the utilization of robotic systems is expected to grow in complex endoscopic procedures, larger series are crucial to evaluate the potential gain and risks related to surgical intervention in this setting.

This study focuses on the 30-day morbidity and mortality of robot-assisted laparoscopic surgery for complex hiatal hernia or problems after previous hiatal hernia or anti reflux surgery. The goal was to provide objective information on surgical risks as background information in preoperative counselling. Data have to be interpreted in relation to the experience of the surgeon. The two surgeons involved in this series had extensive experience and a high annual caseload, and the center involved serves as a tertiary center for large hiatal hernias and recurrent problems after prior surgery.

Robotic assistance was used in repairs of large type 3 or type 4 hiatal hernias, all redo procedures and in conditions that may increase difficulty, such as earlier gastric surgery or high BMI. Currently, this reflects about 50% of patients operated on for reflux and/or hiatal hernia in this center.

MATERIALS AND METHODS

All patients that underwent robot-assisted hiatal hernia repair and/or anti-reflux surgery between January 2011 and July 2017 at the Meander Medical Centre, Amersfoort, the Netherlands were evaluated. This also included all patients undergoing reoperation due to primary procedure failure or postoperative dysphagia within 30 days. Patients with achalasia where a Heller myotomy with concomitant 180° anterior (Dor) fundoplication was performed or patients with a non-hiatal hernia were excluded due to distinct underlying pathophysiology and a different surgical approach.

DATA COLLECTION

Preoperative, intraoperative and postoperative data were collected retrospectively from the electronic patient records. This included patient demographics, American Society of Anesthesiologists (ASA) score, history of previous abdominal surgeries, hiatal hernia type, performed fundoplication and crural reinforcement, operative time, conversion, length of hospital stay, early complications and mortality. The hiatal hernia type was scored by reviewing the radiological, upper endoscopic, and perioperative findings. Hiatal hernias were classified according to the definition stated in the 2013 SAGES guidelines for the management of hiatal hernia (Table 1)¹⁴. Operative times were recorded both as time from incision to skin closure and total time in the OR. Institutional Review Board approval was obtained.

TABLE 1. CLASSIFICATION OF HIATAL HERNIAS

TYPE	DEFINITION
Type I	Sliding hiatal hernias, where the gastroesophageal junction migrates above the diaphragm. The stomach remains in its usual longitudinal alignment and the fundus remains below the gastroesophageal junction.
Type II	Pure paraesophageal hernias (PEH); the gastroesophageal junction remains in its normal anatomic position but a portion of the fundus herniates through the diaphragmatic hiatus adjacent to the esophagus.
Type III	Hernias are a combination of Types I and II, with both the gastroesophageal junction and the fundus herniating through the hiatus. The fundus lies above the gastroesophageal junction.
Type IV	Characterized by the presence of a structure other than stomach, such as the omentum, colon or small bowel within the hernia sac.

STUDY ENDPOINTS

The primary endpoints were postoperative complications and mortality occurring within 30 days after surgery. Any deviation from a normal postoperative course was considered a postoperative complication. All postoperative complications were recorded, meaning that the total number of complications can exceed the number of patients with complications. Complications were scored using the Clavien-Dindo classification of surgical complications¹⁵. Clavien-Dindo scores of IIIb and higher were regarded as major complications. In case of multiple major complications in a single patient, the highest Clavien-Dindo classification was used for further analysis.

STATISTICAL ANALYSIS

Categorical data are presented as absolute numbers or percentages and were analyzed with Pearson's chi-square or Fisher's exact test where appropriate. Continuous data are presented as means with standard deviation for normally distributed data or medians and interquartile ranges (IQR) when not normally distributed. Independent samples t-test and Mann-Whitney U test were used as appropriate to compare the differences between groups.

A double-sided p-value of <0.05 was considered statistically significant. All statistical analyses were carried out using the IBM Statistical Package for Social Sciences for Windows, version 25.0 (SPSS Inc., IBM Corporation, Armonk, NY, USA).

SURGICAL TECHNIQUE

All procedures were carried out by two surgeons using the 4-arm da Vinci Si HD Surgical System (Intuitive Surgical Inc., Sunnyvale, CA). Key steps for hiatal hernia surgery included complete hernia sac dissection and esophageal mobilization to achieve reduction of the herniated contents into a tensionless intra-abdominal position and a tension free position of the GE-junction below the diaphragm. Esophageal dissection was carried out mostly in a blunt fashion, at as much distance as possible from the muscular tube. The hernia sac was not excised routinely to avoid damage to the anterior vagal nerve branches, in these cases it was left intra-abdominally after dissection if it did not interfere with the rest of the procedure. Crural closure was performed with or without the use of mesh or pledgets for reinforcement as deemed necessary by the surgeon and was followed, in most cases, by an anti-reflux procedure. In most cases, a partial fundoplication was performed. In our center, based on recent research^[16–21], the preferred approach is a partial fundoplication. In several patients, a valvuloplasty was performed instead of a fundoplication; a 270-degree intussusception of the esophagus. The procedure used in our center has previously been described in more detail by Tolboom et al²².

Redo procedures were carried out in a similar fashion, however the procedure differed based on preoperative complaints (i.e. reflux symptoms or dysphagia) and anatomical abnormalities (ie. wrap disruption, slipped fundoplication, intra-thoracic wrap migration). Typically, any previously created fundoplication was taken down and a new fundoplication was created. Occasionally, a previously created fundoplication was (partly) preserved or extended and fixated below the diaphragm after the hiatal repair was performed. In select cases of extreme dysphagia, usually occurring after several previous surgeries, widening of the hiatus was performed without creation of a new fundoplication.

RESULTS

PATIENTS

A total of 362 robot-assisted procedures were performed. Patient demographics are presented in Table 2. Median patient age was 65 (IQR 55–71), 71.8% were female. Patients that underwent a primary procedure were significantly older compared to patients in the redo group; 67 years (IQR 58-73) versus 60 years (IQR 51-68). The majority of patients had an ASA score of 2, patients from the primary procedure group had significantly higher ASA scores.

PRIMARY PROCEDURE

Perioperative results are summarized in Table 3. In total, 211 primary procedures were performed. The median total OR time was 149 (IQR 129-170) minutes, the skin-skin surgery duration was 99 (IQR 82–119) minutes. Most patients presented with a symptomatic type 3 or 4 hiatal herniation (45.5% and 38.9%, respectively). Hiatal hernia repair was combined with a fundoplication in all but two patients. In 73.5% an anterior (Dor) fundoplication was created, followed by a posterior (Toupet) fundoplication in 18.0%. Three concomitant procedures were performed; one cholecystectomy and two pyloroplasties. Adequate intra-abdominal esophageal length was achieved by appropriate esophageal mobilization in all repairs, no lengthening procedures were performed.

CONVERSIONS

Conversion to an open procedure was required in seven cases; due to the inability to reduce the hernia because of strong adherence of herniated contents in the thorax (N=3), limited overview of the hiatal region due to adhesions or intra-abdominal fat (N=3), or extent of the hernia where the complete stomach, transversal colon and a significant portion of the small intestine loops herniated intrathoracically (N=1).

TABLE 2. BASELINE CHARACTERISTICS

		TOTAL (N = 362)	PRIMARY PROCEDURE (N = 211)	REDO PROCEDURE (N = 151)	P-VALUE
Age (years, median, IQR)		67 (55–71)	67 (58–73)	60 (51–68)	<0.001 *
Gender (N, %)	<i>Male</i>	102 (28.2%)	58 (27.5%)	44 (29.1%)	0.731
	<i>Female</i>	260 (71.8%)	153 (72.5%)	107 (70.9%)	
ASA (N, %)	1	72 (19.9%)	38 (18.0%)	34 (22.5%)	0.012 *
	2	244 (67.4%)	137 (64.9%)	107 (70.9%)	
	3–4	46 (12.7%)	36 (17.1%)	10 (6.6%)	
Body Mass Index (kg/m², median, IQR)		27 (24–30)	27 (25–31)	27 (24–30)	0.770
Previous intra-abdominal surgery (N, %)	<i>Yes</i>	235 (64.9%)	84 (39.8%)	151 (100.0%)	<0.001 *
	<i>No</i>	127 (35.1%)	127 (60.2%)	0 (0.0%)	
Comorbidities (Yes, N, %)	<i>Cardiac</i>	33 (9.1%)	25 (11.8%)	8 (5.3%)	0.033 *
	<i>Vascular</i>	78 (21.5%)	52 (24.6%)	26 (17.2%)	0.090
	<i>Diabetes</i>	23 (6.4%)	16 (7.6%)	7 (4.6%)	0.257
	<i>Pulmonary</i>	64 (17.7%)	3 (1.8.5%)	25 (16.6%)	0.636
	<i>Neurologic/ psychiatric</i>	17 (4.7%)	11 (5.2%)	6 (4.0%)	0.582
	<i>Gastro-intestinal</i>	8 (2.2%)	5 (2.4%)	3 (2.0%)	1.000
	<i>Urogenital</i>	18 (5.0%)	10 (4.7%)	8 (5.3%)	0.809
	<i>Thrombosis/ coagulation</i>	10 (2.8%)	8 (3.8%)	2 (1.3%)	0.204
	<i>Neuromuscular</i>	4 (1.1%)	2 (0.9%)	2 (1.3%)	1.000
	<i>Endocrinological</i>	23 (6.4%)	16 (7.6%)	7 (4.6%)	0.257
	<i>Musculoskeletal</i>	28 (7.7%)	17 (8.1%)	11 (7.3%)	0.786
	<i>Infectious</i>	1 (0.3%)	1 (0.5%)	0 (-)	1.000

Values are expressed as median (IQR) or number of patients (%). *indicates p-value <0.05.

TABLE 3. PERIOPERATIVE DETAILS

	TOTAL (N=362)	PRIMARY PROCEDURE (N=211)	REDO PROCEDURE (N=151)	P-VALUE	
Surgery duration ¹ (min, median, IQR)	99 (81–120)	99 (82–119)	101 (79–120)	0.932	
Total operative time (min, median, IQR)	148 (128–174)	148 (129–170)	148 (125–176)	0.870	
Hiatal herniation (N, %)					
	<i>No herniation</i>	--	3 (1.4%)	--	
	<i>Type 1</i>		23 (10.9%)		
	<i>Type 2</i>		3 (1.4%)		
	<i>Type 3</i>		96 (45.5%)		
	<i>Type 4</i>		82 (38.9%)		
	<i>Unknown</i>		4 (1.9%)		
Herniated contents (N, %)					
	<i>No organ herniation</i>	125 (34.5%)	29 (13.7%)	96 (63.6%)	<0.001*
	<i>Stomach (partial)</i>	149 (41.2%)	100 (47.4%)	49 (32.5%)	
	<i>Stomach (full) including omentum</i>	63 (17.4%)	59 (28.0%)	4 (2.6%)	
	<i>Stomach (full) including omentum and ≥1 other abdominal organ</i>	25 (7.0%)	23 (10.9%)	2 (1.3%)	
Number of anti-reflux procedures performed previously (N, %)					
	1	--	--	107 (70.9%)	--
	2			38 (25.2%)	
	3			5 (3.3%)	
	4			1 (0.7%)	
Latest fundoplication performed in patient (N, %)					
	<i>Toupet</i>	--	--	54 (35.8%)	--
	<i>Dor</i>			22 (14.6%)	
	<i>Nissen</i>			62 (41.1%)	
	<i>Valvuloplasty</i>			7 (4.6%)	
	<i>Belsey</i>			1 (0.7%)	
	<i>Other</i>			5 (3.3%)	
Performed procedure (N, %)					
	<i>Hiatal hernia repair +fundoplication</i>	316 (87.3%)	209 (99.1%)	107 (70.9%)	<0.001*
	<i>Hiatal hernia repair</i>	16 (4.4%)	2 (0.9%)	14 (9.3%)	
	<i>Fundoplication</i>	21 (5.8%)	0 (0.0%)	21 (13.9%)	
	<i>Other</i>	8 (2.2%)	0 (0.0%)	8 (5.3%)	
	<i>Missing</i>	1 (0.3%)	0 (0.0%)	1 (0.7%)	

Morbidity and mortality in complex robot-assisted hiatal hernia surgery

Fundoplication type performed (N, %)	<i>None</i>	24 (6.6%)	2 (0.9%)	22 (14.6%)	<0.001*
	<i>Nissen</i>	3 (0.8%)	0 (0.0%)	3 (2.0%)	
	<i>Toupet</i>	86 (23.8%)	38 (18.0%)	48 (31.8%)	
	<i>Dor</i>	225 (62.2%)	155 (73.5%)	70 (46.4%)	
	<i>Valvuloplasty</i>	21 (5.8%)	16 (7.6%)	5 (3.3%)	
	<i>360</i>	2 (0.6%)	0 (0.0%)	2 (1.3%)	
	<i>Missing</i>	1 (0.3%)	0 (0.0%)	1 (0.7%)	
Crural reinforcement (N, %)	<i>None</i>	105 (29.0%)	40 (19.0%)	65 (43.0%)	<0.001*
	<i>Pledgets</i>	229 (63.3%)	153 (72.5%)	76 (50.3%)	
	<i>Mesh</i>	27 (7.5%)	18 (8.5%)	9 (6.0%)	
	<i>Missing</i>	1 (0.3%)	0 (0.0%)	1 (0.7%)	
Adhesiolysis (N, %)	<i>Yes</i>	97 (26.8%)	11 (5.2%)	87 (57.6%)	<0.001*
	<i>No</i>	263 (72.7%)	200 (94.8%)	62 (41.1%)	
	<i>Missing</i>	2 (0.6%)	0 (0.0%)	2 (1.3%)	
Conversion (N, %)	<i>Yes</i>	10 (2.8%)	7 (3.3%)	3 (2.0%)	0.531
	<i>No</i>	352 (97.2%)	204 (96.7%)	148 (98.0%)	
Hospital stay (days, median, IQR)		3 (IQR 3–5)	3 (IQR 3–5)	3 (IQR 2–5)	0.025*

¹Surgery duration is defined as time from first incision to skin closure. *indicates p-value <0.05.

POSTOPERATIVE OUTCOMES

Median hospital stay was 3 days (IQR 3–5).

POSTOPERATIVE COMPLICATIONS

Table 4 shows postoperative complications categorized by severity according to the Clavien-Dindo classification. One or more early postoperative complications occurred in 36 (17.1%) patients which comprised 47 complications in total. Eleven (5.2%) patients suffered from major complications.

All recorded postoperative complications classified by diagnosis and treatment are depicted in Table 5. The most common complication was pneumonia which was seen in 13 (6.2%) patients, followed by dysphagia requiring temporary enteral feeding by means of a nasoduodenal feeding tube in seven (3.3%) and atrial fibrillation in five (2.4%) patients. The majority of complications required only conservative treatment or minor interventions. Surgical management of major complications was required in eight patients and was related to abdominal (N=3) or thoracic (N=1) infections, early hernia recurrence (N=2), iatrogenic damage to the small intestine (N=2).

READMISSIONS

There were nine readmissions during the 30-day postoperative period. Six were associated with dysphagia. Three patients required no intervention, their complaints subsided with additional dietary advice. Temporary enteral feeding by means of a nasoduodenal feeding tube was started in two patients; one patient underwent endoscopic balloon dilatation of the gastroesophageal junction. The remaining three readmissions were due to a subphrenic abscess which was successfully drained percutaneously, conservatively treated wound infection, and abdominal complaints.

EARLY RECURRENCES

Evaluation of recurrence was only performed on indication. There were two symptomatic early recurrences of hiatal herniation. Both underwent open correction on postoperative day 2 and 7. The first patient suffered an iatrogenic esophageal perforation in the redo procedure, treated by endoscopic esophageal stent placement and admission to the intensive care unit. Both patients fully recovered.

MORTALITY

Mortality within 30 days after primary surgery was 0.9% (N=2). The first patient, a 86-year-old woman, developed postoperative mediastinitis and underwent emergency surgery on postoperative day 4. An esophageal perforation was diagnosed and treated with endoscopic stent placement and total parenteral feeding. The patient initially responded well but later refused further medical treatment and requested to be transferred to a hospice where she passed away on postoperative

day 30. The second patient, a 78-year-old woman, was readmitted on postoperative day 6 after a previously uncomplicated clinical course due to abdominal pain. After enema application, the patient developed clinical signs of abdominal sepsis and a perforation of the recto-sigmoid was seen upon explorative laparotomy. The patient died on postoperative day 18 due to refractory sepsis unresponsive to operative and antibiotic treatment.

TABLE 4. POSTOPERATIVE COMPLICATION DETAILS BY SEVERITY

	TOTAL (N=362)	PRIMARY PROCEDURE (N=211)	REDO PROCEDURE (N=151)	P-VALUE
No complication	310 (85.6%)	175 (82.9%)	135 (89.4%)	
Minor complication	37 (10.2%)	25 (11.8%)	12 (7.9%)	
Major complication[†]	15 (4.1%)	11 (5.2%)	4 (2.6%)	0.227
CD I	2 (0.6%)	1 (0.5%)	1 (0.7%)	
CD II	28 (7.7%)	19 (9.0%)	8 (6.0%)	
CD IIIa	7 (1.9%)	5 (2.4%)	2 (1.3%)	
CD IIIb	3 (0.6%)	1 (0.5%)	1 (0.7%)	
CD IVa	5 (1.4%)	4 (1.9%)	1 (0.7%)	
CD IVb	6 (1.7%)	4 (1.9%)	2 (1.3%)	
CD V	2 (0.6%)	2 (0.9%)	0 (-)	

[†]Clavien-Dindo scores of IIIb and higher were regarded as major complications.

TABLE 5. POSTOPERATIVE MORBIDITY AND TREATMENT IN THE PRIMARY PROCEDURE GROUP

COMPLICATION		TREATMENT	TOTAL	CD
Minor	<i>Pneumonia</i>	Antibiotics	13	II
	<i>Atrial fibrillation</i>	Antiarrhythmic agents	5	II
	<i>Passage disorders</i>	Nasoduodenal feeding tube	3	IIIa
		Total parenteral nutrition	3	II
		Endoscopic GEJ dilatation	2	IIIa
	<i>Asthma/COPD exacerbation</i>	Corticosteroids, bronchodilators	2	II
	<i>Anemia</i>	Transfusion	1	II
	<i>Wound infection</i>	Conservative treatment	1	I
	<i>Intra-abdominal infection</i>	Percutaneous drainage	1	IIIa
	<i>Pleural effusion</i>	Drainage	1	IIIa
	<i>Iatrogenic damage to other organs</i>	Conservative treatment	1	I
<i>Total</i>		33		
Major	<i>Intra-abdominal infection</i>	Surgical management	3	IIIb, IVb, V
	<i>Intra-thoracic infection</i>	Multiple surgeries with aggressive antibiotic treatment	1	V
	<i>Early recurrence</i>	Surgical repair	2	IIIb
	<i>Iatrogenic GI tract injury</i>	Surgical management	2	IVb
	<i>Pulmonary embolism</i>	Anticoagulants	1	IVa
	<i>Asthma/COPD exacerbation requiring ICU admission</i>	Mechanical ventilation	1	IVa
	<i>Undefined respiratory insufficiency</i>			
	<i>Post-extubation laryngeal edema</i>	Symptomatic treatment	2	IVa, IVb
	<i>Cardiac decompensation</i>	Reintubation, corticosteroids	1	IVa
		Transfer to another hospital	1	IVa
	<i>Total</i>		14	

Values are expressed as number of patients. All postoperative complications were recorded, this results in a total number of complications exceeding the number of patients with complications (e.g. 36). CD – Clavien-Dindo grade, GEJ – gastroesophageal junction.

REDO PROCEDURE

The perioperative results of performed redo procedures are depicted in Table 3. In total, 151 redo procedures were performed. The median total OR time was 148 (IQR 125-176) minutes, while the median surgery time (skin-skin) was 101 (IQR 79-120) minutes. Hiatal hernia repair was performed combined with fundoplication in the majority of patients (70.9%). Hiatal repair alone was performed in 14 (9.3%) patients where a previously created fundoplication was not taken down completely but partly preserved and fixated below the diaphragm. Fundoplication without additional hiatal repair was performed in 21 (13.9%) patients that underwent reoperation either due to persistent reflux or dysphagia after previous surgery. In patients with primarily reflux complaints the preferred type of fundoplication was a 270° posterior (Toupet) fundoplication, where in patients mainly reporting dysphagia a 180° anterior (Dor) fundoplication was created. There were four patients in whom a Toupet fundoplication was created at a previous surgery but later experienced severe dysphagia. In these patients, the fundoplication was taken down and the hiatus was widened by removing one or more crural sutures. In four other redo cases, the procedure was aborted due to dense adhesions.

The most common fundoplication type performed was an anterior (Dor) fundoplication (46.4%), followed by 270° posterior (Toupet) fundoplication (31.8%). In two patients that previously underwent Toupet fundoplication but presented with persisting reflux symptoms a 360° wrap was created. Five concomitant procedures were performed. One patient underwent a concomitant cholecystectomy due to symptomatic cholecystolithiasis. Pyloroplasty was performed in four patients that suffered from severe gastric motility disorders. Adequate intra-abdominal esophageal length was achieved by appropriate mediastinal esophageal mobilization in all repairs, no lengthening procedures were performed.

CONVERSIONS

Conversion to an open procedure was required in three cases due to the inability to laparoscopically reduce the hernia because of strong intra-thoracic adherence of the herniated contents (N=2), or gastric perforation combined with an impaired overview of the anatomy (N=1).

POSTOPERATIVE OUTCOMES

Median hospital stay was 3 days (IQR 2-5).

POSTOPERATIVE COMPLICATIONS

Table 4 shows postoperative complications categorized by severity according to the Clavien-Dindo classification. One or more early postoperative complications occurred in 16 (10.6%) patients which comprised 22 complications in total. Major postoperative complications occurred in 4 (2.6%) patients. Recorded postoperative complications classified by diagnosis and accompanying treatment are shown in Table 6. The most common complications were pneumonia and pneumothorax, which were seen in 5 (3.3%) patients each. The majority of complications required only conservative treatment or minor interventions. Surgical management of complications was required in four patients and was related to thoracic infection (N=2), early hernia recurrence (N=1) and intra-abdominal luxation of a drain which had to be surgically removed (N=1).

READMISSIONS

There were three readmissions during the 30-day postoperative period. One patient presented with gastroparesis for which temporary nasoduodenal tube feeding was started. In one patient anemia was diagnosed and treated by a one-time transfusion. One readmission due to persistent postoperative pain was successfully treated with temporary oral pain medication.

EARLY RECURRENCES

No routine evaluation of recurrence was performed. One symptomatic early recurrence was observed in the redo group. Correction was performed on a postoperative day 3 via laparotomy. Upon surgical revision, takedown of the fundoplication revealed a gastric perforation which was repaired with closure of the defect and an omental patch. Antibiotic and surgical treatment of mediastinitis led to complete recovery.

MORTALITY

None of the patients in the redo group died in the 30-day postoperative period.

DISCUSSION

In this study, we investigated the short-term postoperative outcomes in a large cohort undergoing robot-assisted laparoscopic repair of large symptomatic diaphragmatic hernias and anti-reflux surgery, as well as redo surgery, at a national referral center in the Netherlands.

After primary repair 17.1% of patients experienced complications of any severity, with an incidence of major complications of 5.2%. The 30-day mortality was 0.9%. After redo surgery the incidence of complications of any severity was 10.6%, while the incidence of major complications was 2.6%. No patients died in the 30-day postoperative period after redo surgery. The low number of complications in the redo group was not significantly different from the primary procedure group. There are many factors contributing to morbidity and mortality in surgical outcomes, and it is important to note that the primary repair group had previous intra-abdominal surgery in 39.8% of cases.

TABLE 6. POSTOPERATIVE MORBIDITY AND TREATMENT IN THE REDO PROCEDURE GROUP

COMPLICATION	TREATMENT	TOTAL	CD	
Minor	<i>Pneumonia</i>	Antibiotics	5	II
	<i>Pneumothorax</i>	Drainage	5	IIIa
	<i>Atrial fibrillation</i>	Antiarrhythmic agents	2	II
	<i>Passage disorders</i>	Nasoduodenal feeding tube	1	IIIa
	<i>Asthma/COPD exacerbation</i>	Corticosteroids, bronchodilators	1	II
	<i>Anemia</i>	Transfusion	1	II
	<i>Wound infection</i>	Conservative treatment	1	I
	<i>Hypertension</i>	Antihypertensive agents	1	II
	<i>Total</i>		17	
Major	<i>Intra-thoracic infection</i>	ICU, Surgical drainage	1	IVa
		ICU, Multiple surgeries with aggressive antibiotic treatment	2	IVb
	<i>Early recurrence</i>	Surgical correction	1	IIIb
	<i>Intra-abdominal luxation of a drain</i>	Surgical removal	1	IIIb
	<i>Total</i>		5	

Values are expressed as number of patients. All postoperative complications were recorded, this results in a total number of complications exceeding the number of patients with complication (e.g. 17). CD – Clavien-Dindo grade.

Previous publications have demonstrated the safety and efficacy of robotic assistance in large hiatal hernia repair and anti-reflux surgery, reporting a 30-day postoperative complication rate of 15–23% and mortality rates of 0–2.5%^{8,12,13}. However, currently available literature on this topic is limited to retrospective single institution series with low number of patients, usually operated on over a long period of time leading to a low number of patients per surgeon. Short-term outcomes in our series are comparable to those reported in the literature concerning the conventional laparoscopic approach with a reported overall 30-day morbidity of 4.0–14.5%^{3,23–28} and mortality 0–1.8%^{2,23–29}. However, these numbers should be interpreted with care due to differences in study design, varying number of patients and non-standardized reporting of postoperative complications.

In contrast to the number of randomized controlled trials and reviews comparing conventional laparoscopic to robot-assisted laparoscopic approach in anti-reflux surgery^{11,28–31}, only two recent comparative studies^{7,9} are available regarding the repair of hiatal hernias. Gehrig et al.⁷ conducted a retrospective study including 42 patients where they compared the use of robotic assistance in paraesophageal hernia repair to conventional laparoscopy and open surgery. They showed both laparoscopic approaches to be a safe alternative to open surgery with reduction of intraoperative blood loss, less postoperative complications and shorter hospital stay. In addition, no significant differences in these outcomes were found when comparing the two minimally invasive approaches. This led the authors to conclude that the use of robotic assistance was not superior to conventional laparoscopy in paraesophageal hernia repair. However, this study included only a limited number of patients (12 in the robot group) and did not provide information on hiatal hernia size or type, nor on specific advantages that might be expected from robotic utilization.

The second study, reporting on robot-assisted laparoscopic redo hiatal hernia repair and anti-reflux surgery, was carried out by Tolboom et al.⁹ This study includes a subset of patients from the same cohort analyzed in the current study and the authors of the study are co-authors on the current paper. The study included 75 patients who underwent redo hiatal hernia and anti-reflux surgery with either conventional laparoscopic or robot-assisted approach. They observed a statistically significantly lower conversion rate and shorter hospital stay in the robot-assisted group. The two groups did not differ in mortality, complication rate and symptomatic outcome. The authors concluded that robotic support can be regarded beneficial in redo antireflux surgery, using a minimally invasive approach even in patients that underwent prior open primary repair.

Other reports described robotic assistance of significant value when performing complex, technically demanding procedures^{4,5,12,13}. Although conventional laparoscopy is nowadays the common approach for hiatal hernia repair and anti-reflux

surgery, it can be very difficult. Mediastinal dissection of large diaphragmatic hernias, a history of multiple abdominal surgeries or redo surgery constitute a technical challenge, often influencing the surgeon's decision to favor an open procedure over a laparoscopic approach.

In these cases, the wrist-like motion of instruments and enhanced visualization provided by robotic systems can extend the possibilities of minimally invasive surgery while retaining the advantages of conventional laparoscopy such as reduced blood loss, lower postoperative morbidity and mortality and shorter recovery period when compared to open repair²⁶⁻²⁸. The favorable ergonomic and working position of the surgeon during the complex phase of the intervention may also be of importance when multiple procedures are performed back-to-back by the same surgeon³²⁻³⁸.

The results of this study in a large patient cohort show that a robot-assisted laparoscopic approach can be adopted in large, giant or redo hiatal hernia repair at acceptable complication rates when compared to the available literature on the conventional laparoscopic approach. An uncomplicated postoperative course was observed in the large majority of patients.

This study is a single-arm, single-center retrospective study with limitations inherent to the study design. The present study does not report on outcomes outside of the 30-day postoperative period. Despite these limitations, this report presents the largest series of robot-assisted hiatal hernia repair to date and provides valuable information on the short-term safety and feasibility of this technique.

CONCLUSION

Robot-assisted laparoscopic repair of large and redo hiatal hernias in a tertiary center showed a 2-6% major complication rate, with a less than 1% mortality within 30 days. This provides important background information for preoperative counselling, when gain of quality of life should be balanced against the risk of the surgical intervention.

AUTHOR DISCLOSURES

Dr. Broeders reports personal fees from Johnson & Johnson and Intuitive Surgical. Drs. Mertens, Tolboom, Zavrtnik and Dr. Draaisma have no conflicts of interest or financial ties to disclose.

REFERENCES

1. Robinson B, Dunst CM, Cassera MA, et al. 20 years later: laparoscopic fundoplication durability. *Surg Endosc*. 2015 Sep 9;29(9):2520–4.
2. Luketich JD, Nason KS, Christie NA, et al. Outcomes after a decade of laparoscopic giant paraesophageal hernia repair. *J Thorac Cardiovasc Surg*. 2010 Feb;139(2):395–404, 404.e1.
3. Banki F, Kaushik C, Roife D, et al. Laparoscopic Repair of Large Hiatal Hernia Without the Need for Esophageal Lengthening With Low Morbidity and Rare Symptomatic Recurrence. *Semin Thorac Cardiovasc Surg*. 2017;29(3):418–25.
4. Hanly EJ, Talamini MA. Robotic abdominal surgery. *Am J Surg*. 2004 Oct;188(4A Suppl):19S–26S.
5. Braumann C, Jacobi CA, Menenakos C, et al. Robotic-assisted laparoscopic and thoracoscopic surgery with the da Vinci system: a 4-year experience in a single institution. *Surg Laparosc Endosc Percutan Tech*. 2008 Jun;18(3):260–6.
6. Broeders IAMJ. Robotics: The next step? *Best Pract Res Clin Gastroenterol*. 2014;28(1):225–32.
7. Gehrig T, Mehrabi A, Fischer L, et al. Robotic-assisted paraesophageal hernia repair—a case-control study. *Langenbeck's Arch Surg*. 2013 Jun;398(5):691–6.
8. Brenkman HJF, Parry K, van Hillegersberg R, et al. Robot-Assisted Laparoscopic Hiatal Hernia Repair: Promising Anatomical and Functional Results. *J Laparoendosc Adv Surg Tech*. 2016 Jun;26(6):465–9.
9. Tolboom RC, Draaisma WA, Broeders IAMJ. Evaluation of conventional laparoscopic versus robot-assisted laparoscopic redo hiatal hernia and antireflux surgery: a cohort study. *J Robot Surg*. 2016;10(1):33–9.
10. Müller-Stich BP, Reiter MA, Mehrabi A, et al. No relevant difference in quality of life and functional outcome at 12 months' follow-up—a randomised controlled trial comparing robot-assisted versus conventional laparoscopic Nissen fundoplication. *Langenbeck's Arch Surg*. 2009 May 23;394(3):441–6.
11. Falkenback D, Lehane CW, Lord RVN. Robot-assisted oesophageal and gastric surgery for benign disease: Antireflux operations and Heller's myotomy. *ANZ J Surg*. 2015;85(3):113–20.
12. Galvani CA, Loebl H, Osuchukwu O, et al. Robotic-Assisted Paraesophageal Hernia Repair: Initial Experience at a Single Institution. *J Laparoendosc Adv Surg Tech*. 2016 Apr;26(4):290–5.
13. Draaisma W, Gooszen H, Consten E, et al. Mid-term results of robot-assisted laparoscopic repair of large hiatal hernia: a symptomatic and radiological prospective cohort study. *Surg Technol Int*. 2008;(17):165–70.
14. Kohn K, Price P, Demeester D, et al. SAGES Guidelines for the management of hiatal hernia. *Surg Endosc Interv Tech*. 2013;27(12):4409–28.
15. Dindo D, Demartines N, Clavien P-A. Classification of Surgical Complications. *Ann Surg*. 2004 Aug;240(2):205–13.
16. Broeders JA, Roks DJ, Ahmed Ali U, et al. Laparoscopic anterior 180-degree versus nissen fundoplication for gastroesophageal reflux disease: systematic review and meta-analysis of randomized clinical trials. *Ann Surg*. 2013 May;257(5):850–9.

17. Broeders JAJL, Mauritz FA, Ahmed Ali U, et al. Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. *Br J Surg*. 2010 Sep 16;97(9):1318–30.
18. Broeders JA, Broeders EA, Watson DI, et al. Objective Outcomes 14 Years After Laparoscopic Anterior 180-Degree Partial Versus Nissen Fundoplication. *Ann Surg*. 2013 Aug;258(2):233–9.
19. Du X, Hu Z, Yan C, et al. A meta-analysis of long follow-up outcomes of laparoscopic Nissen (total) versus Toupet (270°) fundoplication for gastro-esophageal reflux disease based on randomized controlled trials in adults. *BMC Gastroenterol*. 2016 Dec 2;16(1):88.
20. Lee CM, Park J-M, Lee HH, et al. Nationwide survey of partial fundoplication in Korea: comparison with total fundoplication. *Ann Surg Treat Res*. 2018 Jun 1;94(6):298.
21. Du X, Wu J-M, Hu Z-W, et al. Laparoscopic Nissen (total) versus anterior 180° fundoplication for gastro-esophageal reflux disease: A meta-analysis and systematic review. *Medicine (Baltimore)*. 2017 Sep;96(37):e8085.
22. Tolboom R, Broeders I, Draaisma W. Robot-Assisted Laparoscopic Hiatal Hernia and Antireflux Surgery. *J Surg Oncol*. 2015 Sep;112(3, SI):266–70.
23. Oor JE, Koetje JH, Roks DJ, et al. Laparoscopic Hiatal Hernia Repair in the Elderly Patient. *World J Surg*. 2016 Jun 25;40(6):1404–11.
24. Castelijns PSS, Ponten JEH, van de Poll MCG, et al. Subjective outcome after laparoscopic hiatal hernia repair for intrathoracic stomach. *Langenbeck's Arch Surg*. 2016;1–10.
25. Prassas D, Rolfs T-M, Schumacher F-J. Laparoscopic repair of giant hiatal hernia. A single center experience. *Int J Surg*. 2015;20:149–52.
26. Schlottmann F, Strassle PD, Farrell TM, et al. Minimally Invasive Surgery Should Be the Standard of Care for Paraesophageal Hernia Repair. *J Gastrointest Surg*. 2017 May 6;21(5):778–84.
27. Zehetner J, DeMeester SR, Ayazi S, et al. Laparoscopic versus open repair of paraesophageal hernia: The second decade. *J Am Coll Surg*. 2011;212(5):813–20.
28. Owen B, Simorov A, Siref A, et al. How does robotic anti-reflux surgery compare with traditional open and laparoscopic techniques: a cost and outcomes analysis. *Surg Endosc*. 2014 May;28(5):1686–90.
29. Morino M, Pellegrino L, Giaccone C, et al. Randomized clinical trial of robot-assisted versus laparoscopic Nissen fundoplication. *Br J Surg*. 2006;93(5):553–8.
30. Draaisma W a, Ruurda JP, Scheffer RCH, et al. Randomized clinical trial of standard laparoscopic versus robot-assisted laparoscopic Nissen fundoplication for gastro-oesophageal reflux disease. *Br J Surg*. 2006 Nov;93(11):1351–9.
31. Müller-Stich BP, Reiter MA, Wente MN, et al. Robot-assisted versus conventional laparoscopic fundoplication: short-term outcome of a pilot randomized controlled trial. *Surg Endosc*. 2007 Sep 13;21(10):1800–5.
32. Elhage O, Challacombe B, Shortland A, et al. An assessment of the physical impact of complex surgical tasks on surgeon errors and discomfort: A comparison between robot-assisted, laparoscopic and open approaches. *BJU Int*. 2015;115(2):274–81.

33. Van Der Schatte Olivier RH, Van't Hullenaar CDP, Ruurda JP, et al. Ergonomics, user comfort, and performance in standard and robot-assisted laparoscopic surgery. *Surg Endosc Other Interv Tech*. 2009;23(6):1365–71.
34. Moore LJ, Wilson MR, McGrath JS, et al. Surgeons' display reduced mental effort and workload while performing robotically assisted surgical tasks, when compared to conventional laparoscopy. *Surg Endosc*. 2015 Sep 27;29(9):2553–60.
35. Stefanidis D, Wang F, Korndorffer JR, et al. Robotic assistance improves intracorporeal suturing performance and safety in the operating room while decreasing operator workload. *Surg Endosc*. 2010 Feb 18;24(2):377–82.
36. Lee GI, Lee MR, Clanton T, et al. Comparative assessment of physical and cognitive ergonomics associated with robotic and traditional laparoscopic surgeries. *Surg Endosc*. 2014 Feb 3;28(2):456–65.
37. Dalager T, Sogaard K, Bech KT, et al. Musculoskeletal pain among surgeons performing minimally invasive surgery: a systematic review. *Surg Endosc*. 2017 Feb 20;31(2):516–26.
38. Lee GI, Lee MR, Green I, et al. Surgeons' physical discomfort and symptoms during robotic surgery: a comprehensive ergonomic survey study. *Surg Endosc*. 2017 Apr 11;31(4):1697–706.

CHAPTER SIX

Operating times in robot-assisted surgery:
let's move on

AC Mertens, TA Burghgraef, ECJ Consten, PM Verheijen,
IAMJ Broeders

Submitted



ABSTRACT

Background

The major downside of robotic surgery in publications is the increased operating time. However, these times are seldomly accurately defined.

Method

The aim of this single center prospective observational study was to validate time registration in robot-assisted low anterior resection (LAR), hiatal hernia repair (HH) and ventral mesh rectopexy (VMR). Precisely defined operating times were compared between times registered by a dedicated researcher, OR and anesthesiology registration.

Results

The observed total OR time (median 125 minutes, IQR 112-149) differed from the OR registration (median 141 minutes, IQR 128-167, $p=.005$) and anesthesiologists' registration (median 122 minutes, IQR 108-147, $p=.005$). The observed skin-to-skin time (median 88 minutes, IQR 68-111) differed significantly from the anesthesiologists' registration (median 83 minutes, IQR 62-101, $p=.001$).

Conclusion

Data from literature and local registration are unreliable, rendering a fair comparison between techniques impossible. Adequate reporting is essential for comparing surgical approaches.

INTRODUCTION

During the past two decades, increased success rates and postoperative outcomes for robot-assisted surgery have been shown for a variety of procedures, with a majority of reports showing comparable outcomes to conventional laparoscopy. The major downside of robotic surgery described in many publications, some of which are as recent as 2019, is the increased operating time associated with the use of a surgical robotic system¹⁻³⁸. However, with growing personal or institutional experience, robot-assisted surgery can be carried out as fast or faster than conventional laparoscopic surgery.

Additionally, most publications reporting on operating time do not provide precise definitions of operating time mentioned in the study (operating time, skin to skin time) or do not define the reported time at all. Moreover, several methods of time registration exist, resulting in additional variation. Furthermore, publications often contain early experience of robot-assisted surgery with a low number of surgeries per year per surgeon^{4,5,27-32,39-41}. These issues are found in most studies presenting operating times on robot-assisted surgery, precluding an unbiased comparison of operating times of robot-assisted surgery with other techniques. These potentially biased data are currently the only available evidence when trying to determine the added value of a robot-assisted surgical system in daily practice.

The aim of this single center observational study is to validate the time registration in robot-assisted surgery in our center, by comparing the digital registration systems used in daily practice with observation of operating time by a dedicated researcher. To achieve this, we selected the three most frequently performed robotic assisted procedures in our center: hiatal hernia repair (HHR), low anterior resections (LAR) and ventral mesh rectopexy (VMR). In addition, we will review the recent literature on the reporting of operating times in these procedures. The results from this study can provide nuance to the currently published data, and we will provide practical handholds for authors aiming to publish on operating times in robot-assisted surgery.

MATERIAL AND METHODS

The aim of this single center prospective observational study was to measure and determine the validity of time registration in three common and frequently reported robot-assisted procedures: LAR, HHR and VMR. Precisely defined OR times were gathered and compared to OR times from the literature comparing robot-assisted and laparoscopic procedures. Patients undergoing robot-assisted HHR, VMR or LAR with the aid of the Da Vinci Si surgical system (Intuitive Surgical, Sunnyvale, CA, USA) in the Meander Medical center were included in this study. The study will include 30 consecutively planned procedures, performed by three surgeons experienced in both laparoscopic and robotic surgery, assisted by a dedicated robotic OR team. All participating surgeons are well into the plateau phase of their learning curve⁴² for robot-assisted surgery (IB >1000, EC >500, PV >500 procedures since 2000). Operating times were registered by a dedicated researcher observing the procedure. These registrations were compared with the digital time registration forms used by the operating team and the time registration system used by the anesthesiologists' team. Ethical and institutional review board approval was obtained, and informed consent requirement was waived.

ENDPOINTS

Operating times including total OR presence, docking time, console time, skin to skin time and surgeon hands-on time for robot-assisted surgeries will be recorded by a researcher observing HHR, VMR and LAR in 30 consecutive patients: 10 for each of the three procedures. The definitions of these time periods are depicted in Table 1. These data will then be compared to the operating teams' time registration and the anesthesiologists' time registration. The anesthesiologists in our center use Anstat (Carepoint Nederland, Ede, Netherlands) for registration of procedures, which is a software package allowing detailed recording and graphing of intra- and postoperative events such as the time of intubation or incision, and measurements such as blood pressure. The OR staff uses Blokplan (Lievestro Software, Ruurlo, Netherlands) for registering and live-tracking surgical procedures. Intraoperatively, the OR staff registers the time spent on different phases of the procedure in Blokplan. This software allows for registration of four important moments in

TABLE 1 – DEFINITIONS OF OPERATING TIME USED IN THE CURRENT STUDY

Total operating time	Starts when the patient enters the OR and ends when the patient leaves the OR.
Skin to skin time	Starts on the first incision and ends after completion of the last skin suture.
Docking time	Starts at the time of the first incision and ends at the moment of completion of robotic instrument insertion.
Console time	Starts when the surgeon is finished docking and enters the console and ends when the surgeon leaves the console to undock the robotic instruments.

a surgical procedure: start of preparation, incision, start of clean-up and end of clean-up. The interval between incision and start of clean-up is used as skin to skin time, while the start of preparation and end of clean-up are used to define total OR time. Docking time and console time are not registered in either system, and as such we are unable to compare these data to the observed times.

The primary endpoint was the difference between the observed times and OR team or anesthesiologists' registration. Differences were calculated for skin to skin time and total OR time. For the purpose of comparison, the time registration as observed by the dedicated researcher will be used as the golden standard. Table 1 depicts the definitions of operating times used in the current study.

STATISTICAL ANALYSIS

Descriptive analysis was performed on total operating time and skin to skin time for all three sources: observation, OR team registration and anesthesiologists' registration. Furthermore, deviation between the observed time and the two registration systems were plotted.

Comparison between observed times and both OR team registration as well as anesthesiologists' registration was achieved using paired tests: parametric data were analyzed using a repeated measures ANOVA, non-parametric data were analyzed using the Friedman test. Post-hoc pairwise comparison was performed using the paired student's t-test for parametric data or the Wilcoxon signed-rank test for non-parametric data, all with Bonferroni adjustment when applicable.

LITERATURE REVIEW

In addition to the statistical analysis above, a concise literature review was performed regarding the published operating times in robot-assisted surgery for the three aforementioned procedures. Publications reporting operating times in robot-assisted surgery related to the three procedures mentioned earlier were selected, scored on accuracy of reporting any operating times and discussed.

RESULTS

Between December 2017 and March 2018, 30 procedures were included. All procedures were completed using the Da Vinci Si robotic system (Intuitive Surgical, Sunnyvale, CA, USA). All planned inclusions were achieved.

Table 2 depicts the registered operating times as observed by the dedicated researcher. Docking was completed in a median of 8 minutes. The draping and set-up of the robotic system did not cause delays when compared to a conventional laparoscopic procedure in any of the procedures because such preparations were done while the anesthesiologist was preparing the patient for surgery in the OR.

SKIN TO SKIN OPERATING TIMES

Table 1 depicts the definition of times used in the current study. The skin to skin times were statistically significantly different between the three different time registration methods, (Friedman test, $\chi^2(2) = 15.948$, $p < .001$). The skin to skin time registrations were statistically significantly different between the observation (median 88 minutes, IQR 68-111) and anesthesiologists' registration (median 83 minutes, IQR 62-101, $p = 0.001$), and between the anesthesiologists' and the OR team registration (median 87 minutes, IQR 70-117, $p < 0.001$). There was, however, no statistically significant difference between the observed times and the OR registration ($p = 0.747$).

The median observed skin to skin operating time was 1 minute shorter than recorded in the OR registration (range: -27 to 16), corresponding to a deviation relative to the total skin to skin time with a median of -0.7% (range: -19.4% to 15.7%). The anesthesiologists' registration showed a median skin to skin operating time that was 6 minutes longer than the observed time (range: -11 to 18) and a corresponding relative median skin to skin time deviation of 8.3% (range: -13.9% to 19.4%). Figure 1 depicts the deviation in skin to skin times per procedure between the observed times and the OR team registration system. Figure 2 depicts the deviation in skin to skin times per procedure between the observed times and those registered by the anesthesiologist.

TABLE 2 – OBSERVED OPERATING TIMES

	DOCKING TIME	CONSOLE TIME	SKIN TO SKIN	TOTAL OPERATING TIME
Low anterior resection	8 [8-11]	63 [45-108]	128 [99-164]	174 [141-205]
Hiatal hernia repair	8 [7-10]	60 [38-69]	79 [63-93]	119 [108-135]
Rectopexy	8 [7-12]	55 [43-66]	75 [60-89]	116 [108-129]

Times are depicted in minutes as median with interquartile range



Figure 1 - Deviation skin to skin time; observed time minus OR registration systems' time. Negative times refer to an overestimation of operating time by the OR registration system. Each bar represents 1 case.

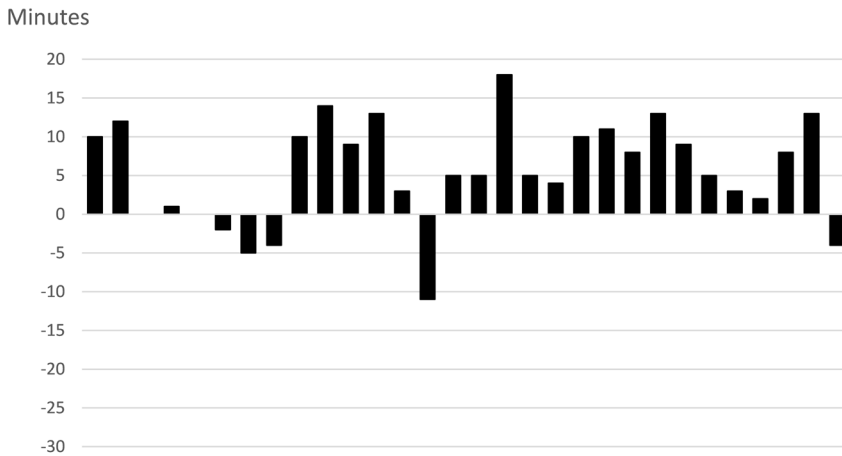


Figure 2 - Deviation skin to skin time; observed time minus anesthesiology registration systems' time. Negative times refer to an overestimation of operating time by the anesthesiology registration. Each bar represents 1 case.

TOTAL OPERATING TIMES

Table 1 depicts the definition of times used in the current study. The total OR times were statistically significantly different, (Friedman test, $\chi^2(2) = 41.043$, $p < .001$). Pairwise comparison showed a statistically significant difference for all three comparisons: observation (median 125 minutes, IQR 112-149) differed significantly from anesthesiologists' registration (median 122 minutes, IQR 108-147, $p = 0.005$), the OR registration (median 141 minutes, IQR 128-167) differed significantly from anesthesiologists' registration ($p < 0.001$) and observation compared with OR registration was significantly different as well ($p = 0.005$).

The median observed total operating time was 12 minutes shorter than what was recorded in the OR registration (range: -53 to 8), with a relative median total operating time deviation of -7.3% (range: -31.9% to 9.1%). Between the observed time and the anesthesiologists' report, the observed median time was 3 minutes shorter (range -6 to 13) with a relative median total operating time deviation of 2.4% (-6.8% to 12.0%). Figure 3 depicts the deviation in total operating time per procedure between the observed time and the time registered by the OR registration system. Figure 4 depicts the deviation in total operating time per procedure between the observed time and the time registered by the anesthesiologists' registration system.

LITERATURE REVIEW

HIATAL HERNIA REPAIR

We selected fifteen studies reporting on the operating times of robot-assisted hiatal hernia surgery^{17-23,25-32}. Five studies discussed the number of surgeons involved and their experience. Four studies^{18,19,25,27,31} described the presence and the experience of a dedicated team. Seven studies^{18,19,25-27,30,31} sufficiently defined the terms "operating time" or "skin to skin time". Three^{19,26,31} reported docking time or set-up time, without providing a definition. None of the studies reported the method used to register the times.

Only two of these studies compared laparoscopic to robot-assisted surgery. Tolboom et al.[23] published a study with data from our center, co-authored by an author from the current study. The authors defined the operating time as 'duration of surgery', without further details. The authors conclude that the median operating times for conventional laparoscopic (median 90, IQR 90-115 minutes) and robot-assisted surgery (median 120, IQR 110-120 minutes) are not statistically different ($p=0.098$). Gehrig et al.[30] provided a detailed definition of operating times, although the method of registration was not described. The authors found operating times for conventional laparoscopy (168, SD 42, range 130-290 minutes) and robot-assisted surgery (172, SD 31, range 115-220 minutes) to be comparable ($p = 0.785$). Neither study mentioned the surgeons' prior experience in robotic surgery.

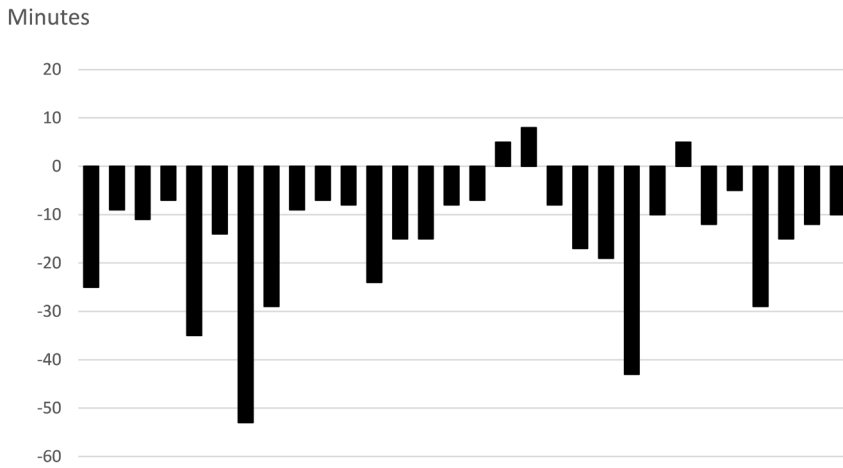


Figure 3 - Deviation total operating time; observation minus OR registration systems' time. Negative times refer to an overestimation of operating time by the OR registration system. Each bar represents 1 case.



Figure 4 - Deviation total operating time; observed time minus anesthesiology registration systems' time. Negative times refer to an overestimation of operating time by the anesthesiology registration. Each bar represents 1 case.

RECTOPEXY

Ten of the selected studies reported on the operating times of robot-assisted ventral (mesh) rectopexy^{6-12,14-16}. Five publications^{6-8,16} reported the number of surgeons involved and their experience. Only one paper⁹ reported on the experience of the surgical team. No study reported the presence of a dedicated team. While no studies reported docking time, four studies^{8,12,15,16} defined and reported preparation time. Skin to skin time was adequately defined and reported in two studies^{8,15}. Nine studies^{6-12,14,16} reported total operating time, though it was defined in only two^{8,16} studies. No studies reported the method used to register the times.

Out of these ten studies, six compared robot-assisted surgery with laparoscopic surgery^{6-12,14-16}. Three studies reported an increase in operating time in the robot-assisted group^{9,11,12}, while the other three studies reported equal operating times^{7,8,10}. The latter studies were published more recently and did not include results of initial experience in robot-assisted ventral rectopexy. Mäkelä-Kaikkonen et al. was the only comparative study to adequately define their operating times and showed a mean skin to skin time of 125 ± 27 min for robot-assisted procedures versus 131 ± 25 min for the laparoscopic group[8].

LOW ANTERIOR RESECTION

We selected twelve studies that discussed operative time of low anterior resections^{2,3,38,4,5,24,33-37}. Four publications^{5,33,34,38} reported on the number of surgeon(s) involved and their experience. None of the publications mentioned the presence of a dedicated team. Docking time was reported in one study²⁴ and one study³⁴ reported preparation time. Neither study provided a definition of these times. Three studies^{4,24,33} defined and reported skin to skin time. Nine studies^{2,3,5,24,34-38} mentioned total operation time, though only one³⁶ defined this. No study reported the method used to register the times.

Out of eight studies comparing laparoscopic rectal resection with robot-assisted rectal resection, six studies showed a longer operating time^{2,3,5,33-35}. Crolla et al.³³ was the only study to adequately define skin to skin time, with a mean of 219 ± 47 minutes for robot-assisted surgery versus 172 ± 48 minutes for laparoscopic surgery. The remaining articles reported mean skin to skin times of 159 to 339 minutes for robot-assisted LAR, and times ranging from 135 to 261 minutes for laparoscopic LAR.

DISCUSSION

The current study aimed to provide information on the validity of time registration in robot-assisted surgery in our center. Additionally, we compared our findings to the scientific canon through a review of the recent literature on this subject.

Through careful observation of surgeries and registration of the OR times by a dedicated researcher, significant deviations in registered times were observed. We found that the observed times and anesthesiology registration were significantly different, with relative deviations of up to 19% of the actual skin to skin time. However, no significant difference was found between observation versus the OR team registration for skin to skin time. This suggests that data from the anesthesiology registration system was not precise enough for obtaining a reliable skin to skin operating time, while the OR registration was relatively accurate. In the case of the total operating time data from both the anesthesiology registration system and the OR team registration were imprecise: total operating time differed significantly between all three methods of obtaining the times (OR team registration, anesthesiology registration and observation). The largest deviation in total registered operating time was seen between observation and OR team registration with deviations of up to an increase of 32% of the actual total OR time, suggesting that the OR registration was the most imprecise method.

Since the main goals of the registration of operating times by the OR team and the anesthesiologists' registry are logistic, financial and medical, they are not necessarily fit for research purposes and perfect registration is unlikely. The difference in deviations of OR team versus anesthesiology registration could perhaps be explained by the method of obtaining these times. With the knowledge that scrub nurses are particularly busy during the entrance and exit of the patient in the OR (during which total OR time needs to be registered), and anesthesiologists (or anesthesiology assistants) are understandably preoccupied with medical care during the incision and closure of the procedure (during which skin to skin time needs to be registered), there is reason to believe that this affected the deviation in operating time and skin to skin time. We would therefore urge authors to describe the method of registering the operating times as one would do with any other potential bias, as this might influence the registered times. In our literature review, we found that the majority of articles did not define the measured operating times, nor did they adequately describe the method of obtaining these times. In addition to this, characteristics considering the operating team, the number of surgeons involved and their experience were inadequately reported for scientific usage. Authors should take into account, and describe, factors influencing operating time such as the experience of the surgeon and the existence and experience of a dedicated OR team.

Over the last two decades, the discussion pertaining the viability of a robotic system in clinical practice has shifted from the safety of the system to a cost-effectiveness analysis. As robotic systems have a high up-front cost and maintenance is more expensive than a comparable laparoscopic set-up, this analysis is undoubtedly relevant. One of the factors determining the cost of such a system is the operating time compared to alternative methods, as time spent in the OR is often a large percentage of the cost of a surgical procedure. The cost-effectiveness analysis, therefore, is partly based on the published scientific canon reporting on operating times. In order to objectively judge the costs of robot-assisted surgery, high-quality data on operating times are required. Our results show a discrepancy in the reported times of the OR registration, anesthesiologist and the true observed times. As our hospital judges operating times based on the OR registration, as most hospitals will, our analysis could justifiably cast doubt on the estimated costs of the robotic system over a conventional laparoscopy set-up.

This study has several limitations. First, having a dedicated researcher in the OR observing the operation times could encourage the OR team or anesthesiology personnel to more actively register the operating times, leading to an underestimation of the differences in time registration. Additionally, we only included 10 patients per procedure, resulting in a relatively small amount of data. It is notable that in spite of this, statistically significant differences were found between the time registration modalities. Furthermore, a full comparison between our observed times and the literature would be inappropriate, considering the low number of patients. Since we did not perform a full systematic review, we did not include all studies considering the three reported procedures. However, by selecting the most important and recent studies of the procedures of interest we did illustrate the lack of clear definitions concerning operating times in surgical studies.

In conclusion, operating times concerning robot-assisted surgery are inadequately defined and reported in the current literature, rendering an adequate comparison between robot-assisted and laparoscopic surgery difficult to impossible. The lack of a clear definition of reported numbers would normally be reason to be extremely cautious when interpreting the outcome of any study, but this does not seem to be the case for operating times. Therefore, we propose a standardization of definitions in the reporting of operating times. First, if operating times are reported, they should be defined in the method section by stating the definition of the beginning and the end of the reported timeframe. Secondly, the method of obtaining these operation times – either by observation or through registration systems – should be described in any future publications. Larger, comparative studies that precisely define and describe their time registration, are required to adequately compare robotic-assisted surgery with other methods. Finally, we would encourage teams

with well-established experience in robot-assisted surgery and adequate volume to report on actual skin to skin times to create updated insights in time consumption in comparison to conventional endoscopic surgery.

COMPLIANCE WITH ETHICAL STANDARDS

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and regional research committee (Medical Research Ethics Committees United, reference number W18.032) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Mertens and Burghgraef. The first draft of the manuscript was written by Mertens and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

Broeders reports personal fees from Johnson & Johnson and Intuitive Surgical. Consten and Verheijen report personal fees from Intuitive Surgical. Mertens and Burghgraef have no conflicts of interest or financial ties to disclose. No funding was received for this study.

REFERENCES

1. Prete FP, Pezzolla A, Prete F, et al. Robotic Versus Laparoscopic Minimally Invasive Surgery for Rectal Cancer. *Ann Surg*. 2018 Jun;267(6):1034–46.
2. Law W-L, Foo D. Comparison of short-term and oncologic outcomes of robotic and laparoscopic resection for mid- and distal rectal cancer. *Surg Endosc*. 2017;31(7):2798–807.
3. Kim MJ, Park SC, Park JW, et al. Robot-assisted Versus Laparoscopic Surgery for Rectal Cancer A Phase II Open Label Prospective Randomized Controlled Trial. 2018;267(2):243–51.
4. Baik SH, Ko YT, Kang CM, et al. Robotic tumor-specific mesorectal excision of rectal cancer: short-term outcome of a pilot randomized trial. *Surg Endosc*. 2008 Jul;22(7):1601–8.
5. Jayne D, Pigazzi A, Marshall H, et al. Effect of Robotic-Assisted vs Conventional Laparoscopic Surgery on Risk of Conversion to Open Laparotomy Among Patients Undergoing Resection for Rectal Cancer. *Jama*. 2017;318(16):1569.
6. Van Iersel JJ, Formijne Jonkers HA, Paulides TJC, et al. Robot-Assisted Ventral Mesh Rectopexy for Rectal Prolapse: A 5-Year Experience at a Tertiary Referral Center. *Dis Colon Rectum*. 2017;60(11):1215–23.
7. Mäkelä-Kaikkonen J, Rautio T, Klintrup K, et al. Robotic-assisted and laparoscopic ventral rectopexy in the treatment of rectal prolapse: a matched-pairs study of operative details and complications. *Tech Coloproctol*. 2013;18(2):151–5.
8. Mäkelä-Kaikkonen J, Rautio T, Pääkkö E, et al. Robot-assisted vs laparoscopic ventral rectopexy for external or internal rectal prolapse and enterocele: a randomized controlled trial. *Color Dis*. 2016;18(10):1010–5.
9. de Hoog DENM, Heemskerk J, Nieman FHM, et al. Recurrence and functional results after open versus conventional laparoscopic versus robot-assisted laparoscopic rectopexy for rectal prolapse: A case-control study. *Int J Colorectal Dis*. 2009;24(10):1201–6.
10. Mehmood RK, Parker J, Bhuvimanian L, et al. Short-term outcome of laparoscopic versus robotic ventral mesh rectopexy for full-thickness rectal prolapse. Is robotic superior? *Int J Colorectal Dis*. 2014;29(9):1113–8.
11. Heemskerk J, De Hoog DENM, Van Gemert WG, et al. Robot-assisted vs. conventional laparoscopic rectopexy for rectal prolapse: A comparative study on costs and time. *Dis Colon Rectum*. 2007;50(11):1825–30.
12. Wong MTC, Meurette G, Rigaud J, et al. Robotic versus laparoscopic rectopexy for complex rectocele: A prospective comparison of short-term outcomes. *Dis Colon Rectum*. 2011;54(3):342–6.
13. Law WL, Foo DCC. Comparison of early experience of robotic and transanal total mesorectal excision using propensity score matching. *Surg Endosc Other Interv Tech*. 2018;0(0):1–7.
14. Inaba CS, Koh CY, Jafari MD, et al. Robotic ventral mesh rectopexy for rectal prolapse: a single-institution experience. *Tech Coloproctol*. 2017;21(8):667–71.
15. Draaisma WA, Nieuwenhuis DH, Janssen LWM, et al. Robot-assisted laparoscopic rectovaginopexy for rectal prolapse: A prospective cohort study on feasibility and safety. *J Robot Surg*. 2008;1(4):273–7.

16. Mantoo S, Podevin J, Regenet N, et al. Is robotic-assisted ventral mesh rectopexy superior to laparoscopic ventral mesh rectopexy in the management of obstructed defaecation? *Color Dis.* 2013;15(8):469–75.
17. Dunnican WJ, Singh TP, Guptill GG, et al. Early robotic experience with paraesophageal hernia repair and Nissen fundoplication: short-term outcomes. *J Robot Surg.* 2008 May 29;2(1):41–4.
18. Mertens AC, Tolboom RC, Zavrtnik H, et al. Morbidity and mortality in complex robot-assisted hiatal hernia surgery: 7-year experience in a high-volume center. *Surg Endosc.* 2019 Jul 22;33(7):2152–61.
19. Ruurda JP, Draaisma WA, van Hillegersberg R, et al. Robot-Assisted Endoscopic Surgery: A Four-Year Single-Center Experience. *Dig Surg.* 2005;22(5):313–20.
20. Sarkaria IS, Latif MJ, Bianco VJ, et al. Early operative outcomes and learning curve of robotic assisted giant paraesophageal hernia repair. *Int J Med Robot.* 2017 Mar;13(1).
21. Seder CW, Cassivi SD, Wigle DA. Navigating the Pathway to Robotic Competency in General Thoracic Surgery. *Innov Technol Tech Cardiothorac Vasc Surg.* 2013;8(3):184–9.
22. Tolboom R, Broeders I, Draaisma W. Robot-assisted laparoscopic hiatal hernia and antireflux surgery. *J Surg Oncol.* 2015;112(3):266–70.
23. Tolboom RC, Draaisma WA, Broeders IAMJ. Evaluation of conventional laparoscopic versus robot-assisted laparoscopic redo hiatal hernia and antireflux surgery: a cohort study. *J Robot Surg.* 2016;10(1):33–9.
24. Kim C-N, Bae SU, Lee S-G, et al. Clinical and oncologic outcomes of totally robotic total mesorectal excision for rectal cancer: initial results in a center for minimally invasive surgery. *Int J Colorectal Dis.* 2016;31(4):843–52.
25. Vasudevan V, Reusche R, Nelson E, et al. Robotic paraesophageal hernia repair: a single-center experience and systematic review.
26. Braumann C, Menenakos C, Rueckert JC, et al. Computer-Assisted Laparoscopic Repair of “Upside-Down” Stomach With the Da Vinci System. *Surg Laparosc Endosc Percutan Tech.* 2005 Oct;15(5):285–9.
27. Brenkman HJF, Parry K, van Hillegersberg R, et al. Robot-Assisted Laparoscopic Hiatal Hernia Repair: Promising Anatomical and Functional Results. *J Laparoendosc Adv Surg Tech.* 2016 Jun;26(6):465–9.
28. Draaisma W, Gooszen H, Consten E, et al. Mid-term results of robot-assisted laparoscopic repair of large hiatal hernia: a symptomatic and radiological prospective cohort study. *Surg Technol Int.* 2008;(17):165–70.
29. Galvani CA, Loebel H, Osuchukwu O, et al. Robotic-Assisted Paraesophageal Hernia Repair: Initial Experience at a Single Institution. *J Laparoendosc Adv Surg Tech.* 2016 Apr;26(4):290–5.
30. Gehrig T, Mehrabi A, Fischer L, et al. Robotic-assisted paraesophageal hernia repair—a case-control study. *Langenbeck’s Arch Surg.* 2013 Jun;398(5):691–6.
31. Morelli L, Guadagni S, Mariniello MD, et al. Robotic giant hiatal hernia repair: 3 year prospective evaluation and review of the literature. *Int J Med Robot.* 2015 Mar;11(1):1–7.
32. Seetharamaiah R, Romero RJ, Kosanovic R, et al. Robotic Repair of Giant Paraesophageal Hernias. *JSL S J Soc Laparoendosc Surg.* 2013;17(4):570–7.

33. Crolla RMPH, Mulder PG, van der Schelling GP. Does robotic rectal cancer surgery improve the results of experienced laparoscopic surgeons? An observational single institution study comparing 168 robotic assisted with 184 laparoscopic rectal resections. *Surg Endosc.* 2018;32(11):4562–70.
34. Jiménez Rodríguez RM, Díaz Pavón JM, de La Portilla de Juan F, et al. Prospective randomised study: Robotic-assisted versus conventional laparoscopic surgery in colorectal cancer resection. *Cir Esp.* 2011;89(7):432–8.
35. Wang G, Wang Z, Jiang Z, et al. Male urinary and sexual function after robotic pelvic autonomic nerve-preserving surgery for rectal cancer. *Int J Med Robot Comput Assist Surg.* 2017;13(1).
36. Feroci F, Vannucchi A, Bianchi P Pietro, et al. Total mesorectal excision for mid and low rectal cancer: Laparoscopic vs robotic surgery. *World J Gastroenterol.* 2016;22(13):3602–10.
37. Perez D, Melling N, Biebl M, et al. Robotic low anterior resection versus transanal total mesorectal excision in rectal cancer: A comparison of 115 cases. *Eur J Surg Oncol.* 2017;44(2):237–42.
38. Lee KY, Shin JK, Park YA, et al. Transanal endoscopic and transabdominal robotic total mesorectal excision for mid-To-low rectal cancer: Comparison of short-Term postoperative and oncologic outcomes by using a case-matched analysis. *Ann Coloproctol.* 2018;34(1):29–35.
39. Patriti A, Ceccarelli G, Bartoli A, et al. Short- and medium-term outcome of robot-assisted and traditional laparoscopic rectal resection. *JLS.* 2009;13(2):176–83.
40. Taggar A, Selim N, Crawford T, et al. Robotic giant paraesophageal hernia repair, the largest single center experience to-date. *Surg Endosc Other Interv Tech.* 2013;27:S390.
41. Sarkaria IS, Latif MJ, Bianco VJ, et al. Early operative outcomes and learning curve of robotic assisted giant paraesophageal hernia repair. *Int J Med Robot Comput Assist Surg.* 2017;13(1).
42. Kassite I, Bejan-Angoulvant T, Lardy H, et al. A systematic review of the learning curve in robotic surgery: range and heterogeneity. *Surg Endosc.* 2019 Feb 28;33(2):353–65.

CHAPTER SEVEN

Value of computed tomography in patients with failed antireflux surgery: Is CT all we need?

RC Tolboom, AC Mertens, BGF Heggelman,
CM Schaefer-Prokop, WA Draaisma, IAMJ Broeders

Submitted



ABSTRACT

Introduction

Laparoscopic antireflux surgery is known to be effective in most patients with gastroesophageal reflux disease (GERD), with a reported success rate of 86–97%. In patients with failed antireflux surgery (e.g., refractory symptoms, or disease recurrence) attempts should be made to determine the underlying mechanism of failure. The aim of this retrospective study was to assess the stand-alone diagnostic value of computerized tomography in correctly classifying the mechanism of failed hiatal hernia surgery. In addition, we compared the accuracy of the evaluation of CT scans by surgeons and radiologists. Operative findings served as reference standard.

METHODS

In a retrospective set up, all patients that underwent redo antireflux surgery between 2011 and 2018 in a single high volume tertiary referral center were included in the data analysis if a CT scan was performed within 6 months prior to redo surgery as part of workup. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), diagnostic odds ratio (DOR) and test accuracy were determined for CT when diagnosing hernia recurrence, migration of the GE-junction, wrap disruption and too-tight fundoplication. Intraoperative findings were regarded as the reference standard.

RESULTS

The highest sensitivity was achieved in diagnosing hiatal hernia recurrence (96%, CI 86–100) with a DOR of 17 (CI 2–138), and NPV of 60% (CI 23–88). The highest specificity (100%, CI 93–100) was achieved when looking for a tight fundoplication. The other CT findings (GE junction migration and wrap disruption) had a lower DOR, respectively 3 (CI 1–10) and 1 (CI 0–18).

CONCLUSION

While computerized tomography is highly sensitive for detecting recurrent hiatal hernia and migration of the gastroesophageal junction, imaging alone is not always sufficient for correctly determining the mechanism of failure in patients with failed antireflux surgery.

INTRODUCTION

Laparoscopic antireflux surgery is known to be effective in most patients with gastroesophageal reflux disease (GERD), with a reported success rate of 86–97%. These patients are symptom-free and no longer require pharmacological treatment for acid reflux¹⁻⁴. Despite this high success rate, several patients suffer from persisting or new-onset complaints following surgery. Some studies report early satiety, bloating, dysphagia, or pain after reduction of the hiatal hernia followed by fundoplication¹⁻⁵. In most patients these symptoms fade in the first weeks, but sometimes they persist. Other patients experience a recurrence of their hiatal hernia and resurgence of their initial symptoms⁶.

The preferred treatment of persisting or new symptoms varies widely and is based upon the underlying pathology. The mechanism of failure should always be properly determined before any decision is made regarding treatment options. A full diagnostic workup consisting of a combination of gastroscopy, manometry, 24-hour pH-monitoring studies, gastric emptying studies and computerized tomography scan (CT) can be considered.

Currently, two different classifications are used to differentiate between the different causes of failure of hiatal hernia repair. In 2007, Horgan et al. proposed a classification based on a detailed analysis of endoscopic, radiologic, and operative findings in a group of 31 patients that underwent surgery. They found that most patients could be categorized in three subcategories: Type 1 can be best described by herniation of the gastro-esophageal (GE) junction. In type 1a failure, the wrap (partially) and the GE junction migrates into the thoracic cavity, whereas in type 1b the fundoplication remains below the diaphragm. Type 2 is characterized as a paraesophageal herniation with the fundoplication and GE junction in the normal position, and type 3 entails a slipped fundoplication⁷.

A second, and more frequently used classification is the Hinder classification. This classification is often used by radiologists when evaluating CT scans. A Hinder type 1 is defined as partial or complete disruption of the wrap, with most cases having a hiatal hernia recurrence. Slippage of the proximal part of the stomach above the diaphragm with the fundoplication in infradiaphragmatic position is considered a Hinder type 2. Slippage of the proximal part of the stomach through the wrap forming an infradiaphragmatic pouch is classified as Hinder type 3. A transdiaphragmatic herniation of the intact wrap is a Hinder type 4^{8,9}.

Other causes of failure not included in the classifications are a patulous or incomplete repair, a tight fundoplication, (peptic) stricture, disturbed esophageal or gastric motility, seroma, abscess or mediastinitis.

Surgical management is usually indicated in patients with underlying anatomical abnormalities and matching therapy resistant symptoms with a substantial burden. In our clinical experience, we regard the computerized tomography as highly suited for determining the mechanism of failure and therefore used it as part of our workup for possible redo-surgery.

The aim of this retrospective study was to assess the stand-alone diagnostic value of computerized tomography in correctly classifying the mechanism of failed hiatal hernia surgery. In addition, we compared the accuracy of the evaluation of CT scans by surgeons and radiologists. Operative findings served as reference standard.

TABLE 1 CAUSES OF FAILURE: PROPOSED NEW CLASSIFICATION

CAUSE OF FAILURE	CLASSIFICATION	
	HINDER	HORGAN
Anatomy (A)		
1 Wrap failure		
<i>a. Disruption of the wrap; partial or complete breakdown of the wrap and, in most cases, a recurrence of hiatal hernia.</i>	I	
<i>b. Patulous or incompetent repair; the wrap is in place and complete but too loose or patulous to adequately construct an effective barrier to reflux</i>		
<i>c. Too tight; the wrap is in place but too tight or long, obstructing the distal esophagus.</i>		
<i>d. Slipped fundoplication; slippage of the proximal stomach through the unbroken wrap creating a pouch below the diaphragm without recurrence of hiatal hernia.</i>	III	III
2 Stomach slippage above the diaphragm; the fundoplication wrap is maintained and remains infradiaphragmatic.	II	
<i>a. The proximal part of the stomach slips and reenters the chest (sliding hernia)</i>		Ib
<i>b. Development of a paraesophageal hernia, often due to disruption of the crural closure</i>		II
3 Transdiaphragmatic wrap herniation; the intact gastric wrap migrates to the chest through the hiatus.	IV	Ia
4 (Peptic) stricture		
Other		
W	Wrong initial diagnosis	
D	Disturbed esophageal/gastric motility	
O	Other diagnosis; seroma / abscess / mediastinitis	
U	Unknown cause of failure / normal anatomy	

METHODS

STUDY GROUP

All patients that underwent redo antireflux surgery between 2011 and 2018 in a single high volume tertiary referral center were included for data analysis if a CT scan was performed within 6 months prior to redo surgery as part of workup.

Intraoperative findings were regarded as the reference standard. The operative reports and, when available, intraoperative video recordings were used to classify the mechanism of failure using a proposed new classification that includes all known causes of failure (Table 1). Data extraction was performed by RT. Patients were excluded if the cause of failure could not securely be determined.

CT scans were acquired in spiral technology with isotropic spatial resolution in all three projections (axial, sagittal and coronal). Images were acquired with 1mm slice thickness and routinely reconstructed with 3mm slice thickness in axial, coronal and sagittal projection using standardized soft tissue windowing. Patients had a small amount of oral contrast immediately before the scan acquisition for demarcation of the upper gastrointestinal tract, no intravenous contrast was given. The scan covered the complete thorax and upper abdomen at least to the level of the portal vein that way ensuring that not only the gastro-esophageal junction but also the anatomy of adjacent organs was sufficiently included.

All CT studies were evaluated after the inclusion period by two independent radiologists (BH and CSP) and two surgeons (IB and WD). The evaluation was performed without knowledge of the clinical context of the patients. The cause of failure was determined, using our more extensive classification, the quality of imaging (insufficient, poor, or high), and certainty of diagnosis (5-point Likert scale). Disagreements regarding the cause of failure were resolved by consensus. Both radiologists have more than 15 years of experience and were specialized in thoracic and abdominal imaging. Both surgeons are experienced upper gastrointestinal surgeons and routinely perform the studied surgical procedure.

DATA ANALYSIS

The results of imaging were compared with the intraoperative findings as a reference. Outcome parameters were sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), diagnostic odds ratio (DOR) and test accuracy.

Data are presented as mean, along with the standard error of the mean for normally distributed data, or median followed by interquartile in square brackets for non-normally distributed data. Statistical analyses were performed using the Wilcoxon signed-ranked test, the Mann-Whitney U test, the χ^2 test, and a dependent

or an independent t-test as appropriate. Inter-observer variability was determined using Cohen's and Fleiss' kappa. P values of <0.05 were regarded as significant. Statistical analyses were performed using commercially available computer software (GraphPad Prism version 8.2.1 for macOS, GraphPad Software, La Jolla (CA), USA and IBM SPSS Statistics version 27.0 for macOS, IBM Corp., Armonk NY, USA).

This study was approved by the the institutional review board and informed consent requirement was waived. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975 and later versions.

RESULTS

One hundred twenty-six patients underwent redo surgery between 2011 and 2018 for new-onset or persisting complaints following primary antireflux surgery. Sixty-six patients (52%) had a computerized tomography scan made as part of their preoperative workup and were included in this study. Most patients were female (67%) and underwent redo surgery 23 [IQR 11–42] months after prior surgery. In ten patients, we were unable to determine the cause of failure (based on intraoperative assessment) due to a combination of missing information in operative reports and unavailability of video recordings. Therefore, these ten patients were excluded from further analysis and the final study group consisted of 56 patients.

REFERENCE STANDARD

During surgery, 49 patients (49/56, 88%) were found to have a hiatal hernia recurrence. The gastroesophageal junction migrated into the thoracic cavity in 40 of these patients (40/49, 82%). The fundoplication's wrap was found to be disrupted by torn sutures in two cases, the fundoplication was too tight in one patient (Table 2).

IMAGE QUALITY AND CONFIDENCE OF DIAGNOSIS RATED BY THE RADIOLOGISTS

The radiologists regarded the quality of the CT scans 'high' in the majority (44/56) of cases, 'low' in 11 and 'insufficient' in only one. Regardless of scan quality, they were 'confident' or 'highly certain' of the diagnosis in most cases (49/56). The single CT scan that was scored to be of 'insufficient' quality resulted in a diagnosis classified as 'most likely' (Figure 1).

The diagnostic results of preoperative CT scans read by radiologists for diagnosing hiatal hernia recurrence, migration of the GE junction, wrap disruption, and a tight fundoplication are shown in Table 3. The highest sensitivity was achieved in diagnosing hiatal hernia recurrence (96%, CI 86–100) with a DOR of 17 (CI 2-138), and NPV

of 60% (CI 23–88). The highest specificity (100%, CI 93–100) was achieved when looking for a tight fundoplication. The other CT findings (GE junction migration and wrap disruption) had a lower DOR, respectively 3 (CI 1–10) and 1 (CI 0–18).

There was a high level of agreement between the surgeons’ and radiologists’ evaluation when diagnosing hiatal hernia recurrence ($\kappa = .879$, CI .617–1.141) and tight fundoplication ($\kappa = 1$, CI .739–1.262). The agreement was moderate for diagnosing a migration of the GE-junction into the thoracic cavity ($\kappa = .470$, CI .208–.732). Only poor agreement was seen for evaluation of wrap disruption ($\kappa = -.318$, CI -.580–.056).

DISCUSSION

Our current study suggests that CT-scan findings alone might be insufficient to correctly classify the mechanism of failure. The largest discrepancy between CT scans and the findings in the operative report is found in patients where the CT imaging showed a disruption of the wrap, often accompanied by a recurrent hiatal hernia (1A).

We found that the condition of the fundoplication at the moment of reoperation was frequently not described in the OR report, and this made matching more difficult. The resulting possible misclassifications generally are of no clinical relevance when the previous fundoplication will be taken down when revising a recurrent hiatal hernia. Relying on CT only may leave thoracic migration or stomach behind at the dorsal side, when complete breakdown is omitted, and repair focused on the anterior side only.

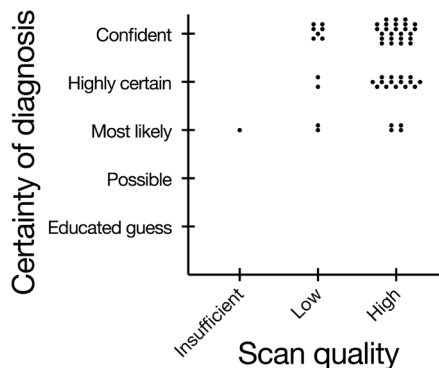


Figure 1. CT scan quality versus certainty of diagnosis.

TABLE 2 CLASSIFICATION OF PATIENTS BASED ON INTRAOPERATIVE FINDINGS (REFERENCE STANDARD) AND PREOPERATIVE CT-SCAN.

	CAUSE OF FAILURE	REFERENCE STANDARD	RADIOLOGISTS' CONSENSUS	SURGEONS' CONSENSUS
Anatomy (A)				
1	Wrap failure			
	<i>a. Disruption of the wrap; partial or complete breakdown of the wrap and, in most cases, a recurrence of hiatal hernia.</i>	2	27	3
	<i>b. Patulous or incompetent repair; the wrap is in place and complete but too loose or patulous to adequately construct an effective barrier to reflux</i>	2	-	-
	<i>c. Too tight; the wrap is in place but too tight or long, obstructing the distal esophagus.</i>	4	1	2
	<i>d. Slipped fundoplication; slippage of the proximal stomach through the unbroken wrap creating a pouch below the diaphragm without recurrence of hiatal hernia.</i>	1	-	-
2	Stomach slippage above the diaphragm; the fundoplication wrap is maintained and remains infradiaphragmatic.			
	<i>a. The proximal part of the stomach slips and reenters the chest (sliding hernia)</i>	-	3	2
	<i>b. Development of a paraesophageal hernia, often due to disruption of the crural closure</i>	9	3	8
3	Transdiaphragmatic wrap herniation; the intact gastric wrap migrates to the chest through the hiatus.	38	18	38
4	(Peptic) stricture	-	-	-
Other				
W	Wrong initial diagnosis	-	-	-
D	Disturbed esophageal/gastric motility	-	-	-
O	Other diagnosis; seroma / abscess / mediastinitis	-	-	-
U	Unknown cause of failure / normal anatomy	-	4	3

TABLE 3 DIAGNOSTIC RESULTS OF CT FOR DIAGNOSING HIATAL HERNIA RECURRENCE, MIGRATION OF GE-JUNCTION, WRAP DISRUPTION, AND TIGHT FUNDOPLICATION.

	HIATAL HERNIA RECURRENCE	GE-JUNCTION MIGRATION	WRAP DISRUPTION	TIGHT FUNDOPLICATION
True positive	47	34	1	1
False positive	4	11	26	0
True negative	3	5	28	52
False negative	2	6	1	3
Sensitivity (95% CI)	96% (86-100)	85% (70-94)	50% (1-99)	25% (1-81)
Specificity (95% CI)	43% (10-82)	31% (11-59)	52% (38-66)	100% (93-100)
Positive predictive value (95% CI)	92% (87-96)	76% (68-82)	4% (1-14)	100% (N/A*)
Negative predictive value (95% CI)	60% (23-88)	45% (23-70)	97% (87-99)	95% (91-97)
Diagnostic odds ratio (95% CI)	17 (2-138)	3 (1-10)	1 (0-18)	N/A*
Diagnostic accuracy (95% CI)	89% (78-96)	70% (56-81)	52% (38-65)	95% (85-99)

*cannot be calculated due to division by 0.

Hiatal hernia recurrence was best detected using CT imaging with a positive predictive value of 92% (CI 87–96). However, this CT finding lacks specificity (43%, CI 10–82) which could be explained due to the high prevalence of hiatal hernia recurrence resulting to a low number of true and false negative findings.

Detection of migration of the gastroesophageal junction was slightly less accurate with a PPV of 76% (CI 68–82) and specificity of 31% (CI 11–59). Some false positives and false negatives could be explained due to difficulty in exactly visualizing the junction on CT, and different circumstances during surgery because of pneumoperitoneum, traction and dissection.

Also, CT scans are made in a relaxed, non-breathing supine position. This may underestimate wrap of stomach migration to the thorax, which could be present in positions with more intra-abdominal upward pressure.

CT imaging performs less well for detecting a too-tight fundoplication. This might be due to a combination of low prevalence and the mode of scanning. In the one true-positive patient, a barium swallow series was performed before the CT scan was made. This enabled the radiologists to easily identify the stenosis due to a tight fundoplication. In all three false-negative tests, a barium swallow was omitted which might explain the failure in detection of a stenosis.

When taking the quality of the CT scans in accord, we did not find any correlation between low-quality scans and the number of false positive and false negative findings. When only looking at low quality scans ($n = 12$), we found one false negative finding when looking at hiatal hernia recurrence, one false negative when looking for a tight fundoplication, two false negatives when evaluating migration of the GE junction and seven false positives when looking for wrap disruption.

As part of the preoperative planning, surgeons often also evaluate CT imaging to assess the anatomy. They look for the presence of a hiatal hernia and attempt to estimate the size of the hiatal hernia. While we did not look at hiatal hernia size estimations in this study, surgeons accurately diagnosed hiatal hernia recurrence in most cases with a kappa of .879. Evaluating the fundoplication itself on CT images proved to be more difficult. Where the radiologists found 27 wrap disruptions on CT, the surgeons only detected two which is reflected in the very poor inter-observer variability ($\kappa = -.318$).

Most previous research regarding failed fundoplication focusses on surgical technique or outcome. Only one prior study looked at the diagnostic process, by evaluating endoscopy in the assessment of failed fundoplication¹⁰. In this study, Juhasz et al. (2011) analyzed the endoscopic findings from a retrospective cohort consisting of 229 patients from a larger database who underwent reoperation after failed fundoplication. Overall, they found the descriptions by the endoscopists to be inadequate and advocate for standardization. In this study, no comparison with intraoperative findings was made¹⁰.

All other diagnostic studies are regarding diagnosing primary hiatal hernia, with several reviews published in the previous years¹¹⁻¹³. Hiatal hernias are generally diagnosed through a selection of three different techniques: barium swallow radiography, endoscopy, manometry and 24-hour pH monitoring. Most patients first undergo endoscopy of the upper gastrointestinal tract in the workup for symptoms of acid reflux. If dilation of the hiatus is present, it can be seen from a retroflexed view during gastroscopy. In patients with recurrent disease however, the anatomy is altered by the fundoplication, which makes evaluation by gastroscopy more difficult¹⁴. It can also be used to detect a too-tight fundoplication or stricture/stenosis which could be endoscopically managed by dilation but offers little information regarding the patency of the fundoplication.

We consider CT scanning to be very valuable in the diagnostic process of failed antireflux surgery, however, we also conclude that no single diagnostic test suffices in all cases in this complex patient category. Often, a patient-tailored combination of diagnostic tests is required for diagnosing the cause of failed antireflux surgery, with endoscopy and manometry/Ph studies as primary additional investigations.

While this study attempts to analyze the sensitivity and specificity of CT imaging in failed antireflux surgery, it is limited by its retrospective nature. We were unable to determine the reference standard based on operative reports and recorded video in 10 patients. While we were able to classify the other results, a prospective study would have increased the accuracy. The next step in researching diagnostic tests after failed antireflux surgery could entail a prospective study where all different diagnostic tests are executed in every patient, enabling researchers to determine the diagnostic value of each diagnostic test.

CONCLUSION

While computerized tomography is highly sensitive for detecting recurrent hiatal hernia and migration of the gastroesophageal junction, imaging alone is not always sufficient for correctly determining the mechanism of failure in patients with failed antireflux surgery.

REFERENCES

1. Stefanidis D, Hope WW, Kohn GP, Reardon PR, Richardson WS, Fanelli RD. Guidelines for surgical treatment of gastroesophageal reflux disease. *Surg Endosc Other Interv Tech.* 2010;24(11):2647-2669.
2. Wileman S. Medical versus surgical management for gastro-oesophageal reflux disease (GORD) in adults. *J Evid Based Med.* 2010;3(3):187.
3. Broeders JAJL, Mauritz FA, Ali UA, et al. Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. *Br J Surg.* 2010;97(9):1318-1330.
4. Tosato F, Marano S, Luongo B, et al. Partial or total fundoplication (with or without division of the short gastric vessels): which is the best laparoscopic choice in GERD surgical treatment? *Surg Laparosc Endosc Percutan Tech.* 2010;20(6):371-377.
5. Rydberg, Ruth, Lundell. Mechanism of action of antireflux procedures. *Br J Surg.* 1999;86(3):405-410.
6. Zhou T, Harnsberger C, Broderick R, et al. Reoperation rates after laparoscopic fundoplication. *Surg Endosc.* 2015;29(3):510-514.
7. Horgan S, Pohl D, Bogetti D, Eubanks T, Pellegrini C. Failed Antireflux Surgery: What Have We Learned From Reoperation? *Arch Surg.* 2007;134:809-817.
8. Hinder RA, Klingler PJ, Perdakis G, Smith SL. Management of the failed antireflux operation. *Surg Clin North Am.* 1997;77(5):1083-1098.
9. Carbo AI, Kim RH, Gates T, Agostino HR. Imaging Findings of Successful and Failed Fundoplication. *RadioGraphics.* 2014;34:1873-1885.
10. Juhasz A, Sundaram A, Hoshino M, Lee TH, Filipi CJ, Mittal SK. Endoscopic assessment of failed fundoplication: a case for standardization. *Surg Endosc.* 2011;25(12):3761-3766.
11. Siegal SR, Dolan JP, Hunter JG. Modern diagnosis and treatment of hiatal hernias. *Langenbeck's Arch Surg.* 2017;402(8):1145-1151.
12. Roman S, Kahrilas PJ. The diagnosis and management of hiatus hernia. *Bmj.* 2014;349(oct23 1):g6154-g6154.
13. Yu H-X, Han C-S, Xue J-R, Han Z-F, Xin H. Esophageal hiatal hernia: risk, diagnosis and management. *Expert Rev Gastroenterol Hepatol.* 2018;12(4):319-329.
14. Jobe BA, Kahrilas PJ, Vernon AH, et al. Endoscopic Appraisal of the Gastroesophageal Valve after Antireflux Surgery. *Am J Gastroenterol.* 2004;99(2):233-243.

PART II

Malignant disease



CHAPTER EIGHT

Morbidity and mortality after curative
gastrectomy in elderly patients;
More harm than good?

AC Mertens, N van der Wielen, HJF Brenkman,
R van Hillegersberg, JP Ruurda, IAMJ Broeders,
JHMB Stoot, MDP Luyer, SM Lagarde, EA Kouwenhoven,
DL van der Peet, WA Draaisma
on behalf of the LOGICA study group

Submitted



ABSTRACT

Background

Surgery for gastric carcinoma is known for its perioperative risks. This study aimed to investigate the predictive value of age on mortality and morbidity in elderly patients undergoing gastrectomy for gastric carcinoma.

Methods

Prospectively collected data from seven Dutch referral centers were used to analyze patients who underwent a curative gastrectomy in the Netherlands between 2000-2015. Elderly patients were defined as patients ≥ 70 years, and as patients ≥ 80 years in two analyses. Postoperative morbidity, 30-day mortality, and overall survival were appraised.

Results

A total of 542 patients were analyzed (224 laparoscopic, 313 open resection), 263 patients < 70 years and 279 patients ≥ 70 years old. Elderly patients had a higher incidence of overall complications (41.8% < 70 versus 53.4% ≥ 70 , $p=0.006$) and 30-day mortality rate (2.7% < 70 versus 8.6% ≥ 70 , $p=0.003$). No difference was found in the incidence of major complications (24.0% < 70 versus 30.8% ≥ 70 , $p=0.078$). The 30-day mortality increased further when comparing patients < 80 (N=461) to ≥ 80 (N=81) years old (4.1% versus 14.8%, $P<0.001$). Both younger subgroups had a significantly higher median overall survival.

Conclusions

Elderly patients are at increased risk of postoperative morbidity and mortality after gastrectomy, while having lower overall survival.

INTRODUCTION

Gastric cancer ranks high on causes of cancer-related deaths worldwide^{1,2}. With an incidence of almost 1 million new cases and more than 700.000 deaths worldwide in 2012, it is the fifth most common malignancy worldwide³. The peak incidence lies after the age of 60, and with rising life expectancies the incidence is expected to increase as well^{4,5}.

The survival of gastric cancer patients has improved significantly with the implementation of neoadjuvant therapy⁶. Additionally, minimally invasive surgical techniques have proven to decrease postoperative complications and improve recovery while retaining oncologic outcomes⁷⁻¹⁴. Even though elderly patients are known to be prone to surgical complications and mortality^{15,16}, these developments can lower the threshold for surgical intervention in the elderly⁹.

Recent publications using data from the Dutch Surgical Colorectal Audit (DSCA) found that older patients have a significantly elevated risk of complications and mortality after surgical resection in colorectal cancer¹⁷⁻¹⁹. These results were consistently observed when using an age cutoff of 70, 75 or 80 years old. The same relationship might very well exist in gastric cancer, as previous studies from outside of Europe have shown²⁰⁻²⁴. While there are several publications and ongoing research projects using data from Western centers, focusing on the optimal treatment of gastric cancer, little contemporary data is available on the effects of age on morbidity and mortality after gastrectomy.

The aim of this multicenter study was to investigate the merits of surgical treatment of gastric cancer in elderly patients compared to a younger population in the Netherlands.

MATERIALS AND METHODS

This multicenter cohort study included data from seven referral centers for gastric cancer surgery in the Netherlands. All data were extracted from prospectively collected institutional databases. This study was approved by the ethics committee of the University Medical Center Utrecht, informed consent requirement was waived for this study.

PATIENT CHARACTERISTIC AND CLINICAL DATA

Patients who underwent potentially curative (cT1-4aN0-3M0) gastrectomy for gastric adenocarcinoma between 2000 and 2015 were included in this study. Patient characteristics, neo-adjuvant therapy, surgical techniques, pTNM (7th edition²⁵) and postoperative outcomes were analyzed.

OUTCOME DATA

The primary endpoints of this study were postoperative morbidity and mortality. Complications were graded according to the Clavien-Dindo classification scale of surgical complications²⁶. Major complications were defined as a Clavien-Dindo score ≥ 3 . The cutoff point for dividing the cohort in young versus older population was set at the age of 70. Additionally, subgroup analysis was performed using a cutoff point of 80 years old. Survival was calculated from the time of surgery to death of any cause.

STATISTICAL ANALYSIS

All data were processed and analyzed using the IBM Statistical Package for Social Sciences, version 23.0 for Macintosh (SPSS, Chicago, IL). Independent t-test, Mann-Whitney U test or X^2 test were performed on baseline characteristics where applicable. Survival curves were generated using the Kaplan-Meier method, differences between groups were tested using the log-rank, Tarone-Ware and Breslow tests. Univariable logistic regression analysis was performed to identify prognostic independent variables related to 30-day mortality and complications. Relevant predictive variables with a p-value of less than 0.050 were selected for inclusion in a multiple logistic regression analysis. A double-sided p-value of <0.050 was considered statistically significant.

RESULTS

A total of 542 patients underwent (sub)total gastrectomy with curative intent between 2000 and 2015 (Table 1). The median follow-up period was 2.21 years, ranging from 0-14.1 years. Patients were divided in two groups based on age, with the cutoff point set at the age of 70. The population <70 years old consisted of 263 patients, the population ≥ 70 years old consisted of 279 patients.

The median age at time of surgery was 70.5 years (62.4-77.1). Baseline analysis showed several significant differences between groups (Table 1). Patients older than 70 years of age had more comorbidities (65.4% <70 versus 83.9% ≥ 70 , $p < 0.001$), a higher American Society of Anesthesiologists (ASA) classification ($p < 0.001$) and received neo-adjuvant treatment less often (75.3% <70 versus 35.5% ≥ 70 , $p < 0.001$). In addition, the incidence of multiple comorbidities was significantly higher in older patients.

POSTOPERATIVE RESULTS

There were no significant differences in gender, pTNM stage (7th TNM Edition[25]), tumor location or surgical approach across groups. The postoperative results are depicted in Table 2. Older patients were more likely to undergo a subtotal gastrectomy ($p < 0.001$). Complications occurred more frequently in the older population (41.8%

<70 versus 53.4% \geq 70, $p=0.006$). However, there was no statistical difference in the incidence of major complications compared to minor or no complications (24.0% <70 versus 30.8% \geq 70, $p=0.078$). In older patients, hospital stay was longer (median 9 days (IQR 7-14) <70 versus 10 days (7-17) \geq 70, $p=0.039$), and 30-day mortality was higher (2.7% <70 versus 8.6% \geq 70, $p=0.003$). Radical resection (R0) was comparable between both groups (89.4% <70 versus 90.0% \geq 70, $p=0.967$).

SUBGROUP ANALYSIS: NEO-ADJUVANT TREATMENT

Subgroup analysis on patients >70 years showed that patients not receiving neo-adjuvant treatment (N=180) had a higher 30-day mortality rate (2.0% after receiving neo-adjuvant treatment versus 12.2% after not receiving neo-adjuvant treatment, $p=0.004$), required Intensive Care Unit (ICU) treatment more often (13.1% after receiving neo-adjuvant treatment versus 19.4% after not receiving neo-adjuvant treatment, $p=0.038$) and had a higher ASA classification ($p=0.028$), possibly indicative of a higher rate of comorbidity or frailty in this group.

SUBGROUP ANALYSIS: 80+

Subgroup analysis on octogenarians (N=81) showed a comparable prevalence of comorbidities (74.0% <80 versus 80.2% \geq 80, $p=0.229$). However, a higher median ASA classification ($p<0.001$) was observed. Although no difference was found in the incidence of major complications, the absolute number of complications increased with age (45.1% <80 versus 63.0% \geq 80, $p=0.002$). Furthermore, the 30-day mortality in octogenarians was significantly higher (4.10% <80 versus 14.80% \geq 80, $p<0.001$).

REGRESSION ANALYSIS

Univariable logistic regression analysis was performed on 30-day mortality and major complications. The number of events (ie. complications) limits the amount of dependent variables that can be entered in the analysis, and as such comorbidities have not been used in the regression analysis as this would violate statistical conventions. 30-day mortality was associated with age >70, ASA III-IV and neo-adjuvant treatment. Major complications were associated with type of resection, surgical approach, ASA-classification and neo-adjuvant treatment. In the multiple logistic regression analysis on 30-day mortality, patients receiving neo-adjuvant treatment had a lower risk of 30-day mortality, ASA III-IV was associated with an increased risk. The age at time of surgery did not reach statistical significance (Table 3).

Multiple logistic regression analysis on major complications versus no or minor complications (Table 4) showed an increased risk of major complications when undergoing a total gastrectomy. ASA III-IV patients had a significantly higher risk of major complications when compared to ASA I-II patients. Minimally invasive surgery reduced the risk of major complications. The age at time of surgery did not reach statistical significance in the univariable regression analysis.

Survival analysis using Kaplan-Meier analysis was carried out on overall survival with age as the dependent variable, using the cutoff point of 70 years old (Figure 1). The percentage of censored cases present in the <70 (58.9%) and \geq 70 (52.5%) groups were similar. Patients 70 years and older had a median survival of 2.9 years, which was significantly lower compared to the younger population in which a median survival of 4.0 years in younger patients. The log rank test comparing survival between the groups did not reach statistical significance ($X^2(1) = 3.275$, $p=0.070$). However, both the Breslow ($X^2(1) = 5.292$, $p=0.021$) and Tarone-Ware ($X^2(1) = 4.520$, $p=0.034$) tests achieved significant p values.

Additionally, Kaplan-Meier survival analysis was performed on the dichotomous variable for age using a cutoff point of 80 years of age (Figure 2). The percentage of censored cases present in the <80 (57.8%) and \geq 80 (43.2%) varied. Younger patients had a higher median survival compared to elderly patients (3.66 versus 2.03 years). The log rank test demonstrated a better survival for patients aged <80 years ($X^2(1) = 7.940$, $p=0.005$). The log rank test provides data on later time points compared to the Breslow and Tarone-Ware tests, which provide more information on earlier time points and weights the data based on number at risk at any given time. Taking this into account, these results fit the survival curves; survival appears to diverge in the first years postoperatively and converges at the end of our follow-up period.

TABLE 1 - BASELINE CHARACTERISTICS

		< 70 (N=263)		≥ 70 (N=279)		P-VALUE
		N	%	N	%	
Patients (N)		263	48.52%	279	51.48%	
Age (years, mean)		60.04		77.32		0.000*
BMI (Kg/M2, mean)		25.32		25.21		0.785
GENDER	<i>Male</i>	160	60.8%	162	58.1%	0.626
	<i>Female</i>	103	39.2%	115	41.2%	
ASA	<i>I</i>	48	18.6%	14	5.2%	0.000*
	<i>II</i>	165	64.0%	149	55.4%	
	<i>III</i>	43	16.7%	98	36.4%	
	<i>IV</i>	2	0.8%	8	3.7%	
Neo-adjuvant treatment	<i>Yes</i>	198	75.3%	99	35.5%	0.000*
	<i>No</i>	65	24.7%	180	64.5%	
Comorbidities	<i>Yes</i>	172	65.4%	234	83.9%	0.000*
	<i>No</i>	91	34.6%	45	16.1%	
Type of comorbidity	<i>Cardiac</i>	45	17.1%	128	45.9%	0.000*
	<i>Vascular</i>	86	32.7%	135	48.4%	0.000*
	<i>Diabetes</i>	42	16.0%	67	24.0%	0.020*
	<i>Pulmonic</i>	48	18.3%	47	16.8%	0.652
	<i>Neurological</i>	32	12.2%	51	18.3%	0.048*
	<i>GI tract</i>	31	11.8%	36	12.9%	0.693
	<i>Urological</i>	15	5.7%	39	14.0%	0.001*
	<i>Thrombosis</i>	14	5.3%	14	5.0%	0.873
	<i>Muscular</i>	11	4.2%	14	5.0%	0.644
	<i>Endocrine</i>	23	8.7%	12	4.3%	0.035*
	<i>Infectious</i>	2	0.8%	9	3.2%	0.042*
Tumor location	<i>Fundus / cardia</i>	55	20.9%	35	12.5%	0.062
	<i>Corpus</i>	70	26.6%	79	28.3%	
	<i>Antrum</i>	93	35.4%	126	45.2%	
	<i>Pylorus</i>	18	6.8%	15	5.4%	
	<i>Entire stomach</i>	6	2.3%	4	1.4%	
	<i>Remnant stomach</i>	3	1.1%	8	2.9%	
	<i>Cardia</i>	1	0.4%	1	0.4%	
	<i>Undefined</i>	17	6.5%	11	3.9%	

* indicates P value <0.05

TABLE 2 - POSTOPERATIVE RESULTS

		< 70 (N=263)		≥ 70 (N=279)		P-value
		N	%	N	%	
SURGICAL APPROACH (N,%)	<i>Open</i>	141	53.6%	172	61.6%	0.065
	<i>Minimally invasive</i>	119	45.2%	105	37.6%	
	<i>Unknown</i>	3	1.1%	2	0.7%	
TYPE OF RESECTION (N,%)	<i>Total stomach</i>	137	52.1%	101	36.2%	0.001*
	<i>Subtotal</i>	123	46.8%	173	62.0%	
	<i>Wedge</i>	0	0.0%	2	0.7%	
	<i>Proximal</i>	2	0.8%	2	0.7%	
	<i>Unknown</i>	1	0.4%	1	0.3%	
PT-STADIUM (N,%)	<i>T0</i>	12	4.6%	10	3.6%	0.872
	<i>Tcis</i>	4	1.5%	3	1.1%	
	<i>T1</i>	45	17.1%	46	16.5%	
	<i>T2</i>	52	19.8%	65	23.3%	
	<i>T3</i>	111	42.2%	111	39.8%	
	<i>T4</i>	38	14.4%	42	15.1%	
	<i>Tx</i>	1	0.4%	2	0.7%	
PN-STADIUM (N,%)	<i>N0</i>	114	43.3%	118	42.3%	0.056
	<i>N1</i>	49	18.6%	66	23.7%	
	<i>N2</i>	42	16.0%	41	14.7%	
	<i>N3A</i>	37	14.1%	45	16.1%	
	<i>N3B</i>	20	7.6%	7	2.5%	
	<i>Nx</i>	1	0.4%	2	0.7%	
COMPLICATIONS	<i>Yes</i>	110	41.8%	149	53.4%	0.006*
CLAVIEN DINDO	<i>No complication</i>	153	58.2%	130	46.6%	0.011*
	<i>1</i>	14	5.3%	17	5.7%	
	<i>2</i>	31	11.8%	45	15.4%	
	<i>3</i>	20	7.6%	23	8.2%	
	<i>4</i>	35	13.3%	36	12.9%	
	<i>5</i>	8	3.0%	27	9.7%	
	<i>Unknown</i>	3	1.1%	1	0.4%	
MAJOR COMPLICATIONS	<i>CD ≥ 3</i>	63	24.0%	86	30.8%	0.078
RADICAL RESECTION	<i>R0</i>	235	89.4%	251	90.0%	0.967
	<i>R+</i>	22	8.4%	23	8.2%	
	<i>Rx</i>	6	2.3%	5	1.8%	

		< 70 (N=263)		≥ 70 (N=279)		P-value
		N	%	N	%	
READMISSION <30 DAYS	Yes	20	7.6%	21	7.5%	0.973
HOSPITAL STAY (MEDIAN (IQR), DAYS)		9 (7-14)		10 (7-17)		0.039*
ICU STAY (MEDIAN (IQR), DAYS)		0 (0-1)		0 (0-1)		0.114
ICU ADMISSION	>1 day	165	32.3%	159	35.5%	0.056
30 DAYS MORTALITY	Yes	7	2.7%	24	8.6%	0.003*

* indicates P value <0.05; ICU, Intensive Care Unit; IQR

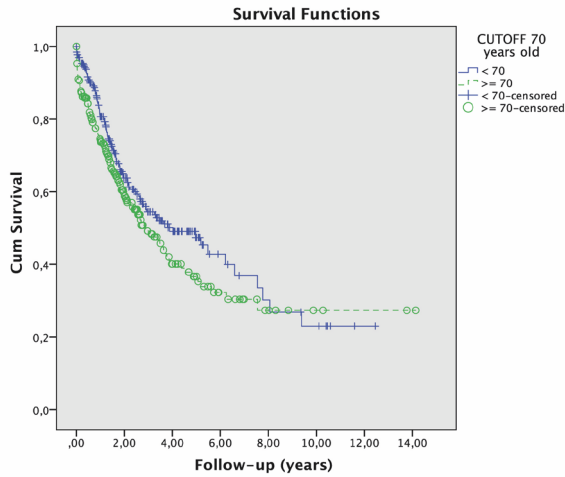


Figure 1 - Kaplan-Meier analysis using a cutoff point for age of 70 years old

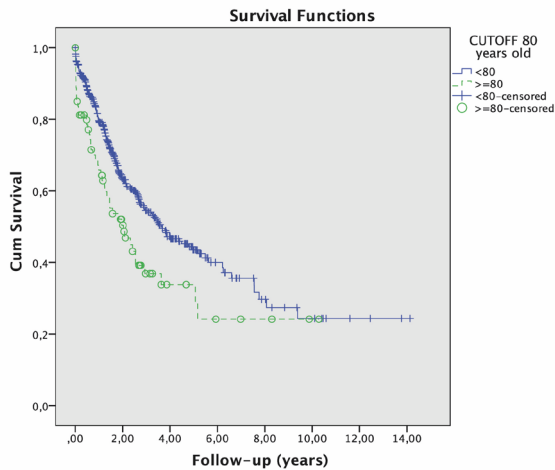


Figure 2 - Kaplan-Meier analysis using a cutoff point for age of 80 years old

TABLE 3 – LOGISTIC REGRESSION ANALYSIS FOR 30-DAY MORTALITY

30-DAY MORTALITY					
Factors	Univariable			Multivariable	
	OR (95% CI)	P	OR (95% CI)	P	
Age (≥ 70)	3.441 (1.457-7.128)	0.005*	1.532 (0.593-3.958)		0.378
BMI	0.944 (0.859 - 1.039)	0.241			
Gender (female)	0.694 (0.320 - 1.503)	0.354			
ASA	<i>III-IV</i>	5.065 (2.363 - 10.856)	0.000*	3.541 (1.600-7.837)	0.002*
Procedure	<i>MIS</i>	0.582 (0.261-1.296)	0.185		
Type of resection	<i>Subtotal</i>	0.740 (0.227- 1.003)	0.051		
Neo-adjuvant		0.182 (0.073 - 0.450)	0.000*	0.258 (0.097-0.688)	0.007*

* indicates P value <0.05; MIS, Minimally invasive surgery; OR, Odds Ratio

TABLE 4 – LOGISTIC REGRESSION ANALYSIS FOR THE RISK OF MAJOR COMPLICATIONS

MAJOR COMPLICATIONS					
Factors	Univariable			Multivariable	
	OR (95% CI)	P	OR (95% CI)	P	
Age (≥ 70)	1.377 (0.830 - 2.285)	0.216			
BMI	0.980 (0.937 - 1.026)	0.393			
Gender (female)	0.792 (0.536 - 1.169)	0.240			
ASA	<i>III-IV</i>	2.426 (1.620 - 3.633)	0.000*	2.267 (1.459 - 3.523)	< 0.001*
Procedure	<i>MIS</i>	0.453 (0.301 - 0.682)	0.000*	0.375 (0.240 - 0.586)	< 0.001*
Type of resection	<i>Subtotal</i>	0.416 (0.283 - 0.612)	0.000*	0.302 (0.195 - 0.468)	< 0.001*
Neo-adjuvant		0.675 (0.462 - 0.985)	0.042*	0.678 (0.441 - 1.045)	0.078

* indicates P value <0.05; MIS, Minimally invasive surgery; OR, Odds Ratio

DISCUSSION

With the increasing age in general, finding the optimal treatment regimen for gastric cancer remains a priority. In the Netherlands, 50% of patients treated for gastric cancer are 70 years or older²⁷. Since an age of 70 or older is known as an independent predictor of complications, early mortality and prolonged hospital stay after several other types of surgery¹⁵, there is a need for optimal treatment of these older patients while retaining quality of life. While (neo-)adjuvant treatment has shown increased disease free survival⁶, surgery remains the standard of care. Several advances have been made in the Netherlands in gastric cancer surgery. First, the minimum number of yearly performed gastrectomies per center has been increased from 10 in 2012 to 20 as of 2013 leading to a reduced number of centers performing this procedure with increased experience in each center. Second, minimally invasive surgical treatment in gastric cancer has been proven to decrease the risk of short term mortality and morbidity with similar oncologic outcomes⁷⁻¹⁴, making surgical resection of gastric cancer more accessible to the elderly population. The third factor accelerating improvement of care is the initiation of the Dutch Upper-GI Cancer Audit in 2011, allowing centers to compare their results, leading to improved standardization of care and outcomes^{27,28}.

Earlier publications reported an increased mortality with older age in colonic cancer surgery in the Netherlands when using an age cutoff of 70 years old^{18,19}. We hypothesized that surgical interventions in gastric cancer might have the same effect. Several recent publications regarding surgical treatment of gastric cancer in elderly showed a significantly higher risk of postoperative complications or lower survival when using similar age-based limits for subgroup analysis^{10,20-24,29,30}, however other authors found no differences and advocate an aggressive approach in elderly patients³¹⁻³³. These publications are not necessarily applicable to the Dutch population due to considerable differences in patient characteristics, treatment regimens and stage of disease due to the lack of a screening program^{11,34}. The present study made it possible to analyze a large cohort of patients undergoing a surgical resection in the Netherlands.

This study showed a higher incidence of perioperative complications and mortality with increasing age. Both when using an age cutoff of 70 and 80 years old, the older subgroups experienced higher complication rates, although no difference was found in the incidence of major complications. A 30-day mortality of 2.7% was seen in patients under 70 versus 8.6% in patients above 70 years old, increasing to 14.80% in patients older than 80 years of age. However, when correcting for confounders in the regression analysis, age at time of surgery did not reach statistical significance. Additionally, long-term survival was significantly lower for both older groups.

The multiple logistic regression model as well as the comparative analysis showed neo-adjuvant treatment as a significant predictor of a lower 30-day mortality, while an ASA classification of III or IV correlated with a higher 30-day mortality. In daily practice, patients in suboptimal condition do not receive neoadjuvant treatment and instead only undergo resection, which we suspect to be the reason for this correlation. Although an increase in complications or mortality is to be expected in older patients due to their increased comorbidities and diminished physical reserves, as in part shown by the increased ASA classification, the large increase in morbidity and mortality with age in our cohort is noteworthy. Our data did not include information on the physical condition of patients or presence of frailty, and multiple regression analysis using comorbidities was not statistically feasible. It is plausible that the age of the patient itself is not the biggest predictive factor for mortality or morbidity, but ASA classification and other factors related to the patients' condition are more suited.

The results of this study have to be interpreted in light of several limitations. Given that our database only includes those patients who underwent surgery, these results are by design limited in its applicability to the general population with gastric cancer. The choice between offering or withholding surgical treatment from patients is – apart from nationwide guidelines - partly based on the professional judgment of the patient's condition by the local multidisciplinary team. This indicates that selection bias cannot be ruled out. Unfortunately, due to the relatively low number of complications, a multiple regression analysis correcting for comorbidities was not possible in the current database. Additionally, no data on complications are registered beyond 30 days. A strong aspect of this study is that there was no selection bias beyond the initial decision to include surgery as part of the treatment, as all patients who underwent intended curative resection were included. For professionals deciding whether or not to offer the option of surgery to the patient, this study provides the team with clear information on morbidity and mortality in elderly patients.

CONCLUSION

Patients above 70 years of age are at significantly increased risk of complications and early mortality after surgical treatment of gastric cancer, while having a lower long-term survival. These risks are further increased in octogenarians. The decision for a surgical resection in patients over 80 years should be made with caution, and these results should be taken into account when counseling patients preoperatively.

CONFLICT OF INTEREST

Broeders reports personal fees from Johnson & Johnson and Intuitive Surgical. The remaining authors declare no conflict of interest.

ACKNOWLEDGEMENTS

Dr. P.C.M. Pasker-de Jong, for her assistance in the statistical analysis.

COLLABORATORS

The LOGICA Study Group members are the authors of this article and the following researchers; MJ van Det, BPL Wijnhoven, GAP Nieuwenhuijzen, JJW Tegels.

HUMAN RIGHTS STATEMENT

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

INFORMED CONSENT

Ethical review board approval was obtained and informed consent requirement was waived for this study.

REFERENCES

1. Jemal A, Bray F, Ferlay J. Global Cancer Statistics: 2011. *CA Cancer J Clin.* 1999;49(2):1,33-64.
2. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin.* 2015 Mar;65(2):87-108.
3. GLOBOCAN 2012 (IARC). Estimated Incidence, Mortality and Prevalence Worldwide in 2012. Estimated Incidence, Mortality and Prevalence Worldwide in 2012. [cited 2017 Aug 1]. Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx?cancer=stomach
4. Katai H, Sasako M, Sano T, et al. Gastric cancer surgery in the elderly without operative mortality. *Surg Oncol.* 2004;13(4):235-8.
5. Marugame T, Dongmei Q. Comparison of Time Trends in Stomach Cancer Incidence (1973-1997) in East Asia, Europe and USA, from Cancer Incidence in Five Continents Vol. IV-VIII. *Jpn J Clin Oncol.* 2007 Mar 1;37(3):242-3.
6. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med.* 2006 Jul 6;355(1):11-20.
7. Lee S-I, Choi Y-S, Park DJ, et al. Comparative Study of Laparoscopy-Assisted Distal Gastrectomy and Open Distal Gastrectomy. *J Am Coll Surg.* 2006 Jun;202(6):874-80.
8. Zhou C-J, Chen F-F, Zhuang C-L, et al. Feasibility of radical gastrectomy for elderly patients with gastric cancer. *Eur J Surg Oncol.* 2016 Feb;42(2):303-11.
9. Kwon IG, Cho I, Guner A, et al. Minimally invasive surgery as a treatment option for gastric cancer in the elderly: comparison with open surgery for patients 80 years and older. *Surg Endosc.* 2015 Aug 6;29(8):2321-30.
10. Gretschel S, Estevez-Schwarz L, Hünerbein M, et al. Gastric cancer surgery in elderly patients. *World J Surg.* 2006;30(8):1468-74.
11. Wielen N Van Der, Straatman J, Cuesta MA, et al. Short - term outcomes in minimally invasive versus open gastrectomy : the differences between East and West . A systematic review of the literature. *Gastric Cancer.* 2018;21(1):19-30.
12. Yu J, Hu J, Huang C, et al. The impact of age and comorbidity on postoperative complications in patients with advanced gastric cancer after laparoscopic D2 gastrectomy: Results from the Chinese laparoscopic gastrointestinal surgery study (CLASS) group. *Eur J Surg Oncol.* 2013;39(10):1144-9.
13. Kim W, Kim HH, Han SU, et al. Decreased morbidity of laparoscopic distal gastrectomy compared with open distal gastrectomy for stage I gastric cancer: Short-term outcomes from a multicenter randomized controlled trial (KLASS-01). *Ann Surg.* 2016;263(1):28-35.
14. Brenkman HJF, Gisbertz SS, Slaman AE, et al. Postoperative Outcomes of Minimally Invasive Gastrectomy Versus Open Gastrectomy during the Early Introduction of Minimally Invasive Gastrectomy in the Netherlands. *Ann Surg.* 2017;266(5):831-8.
15. Polanczyk CA, Marcantonio E, Goldman L, et al. Impact of age on perioperative complications and length of stay in patients undergoing noncardiac surgery. *Ann Intern Med.* 2001 Apr 17;134(8):637-43.
16. Clegg A, Young J, Iliffe S, et al. Frailty in Older People. *Lancet.* 2014;381(9868):752-62.

17. Gietelink L, Wouters MWJM, Bemelman WA, et al. Reduced 30-Day Mortality After Laparoscopic Colorectal Cancer Surgery. *Ann Surg.* 2016 Jul;264(1):135–40.
18. Hamaker ME, Schiphorst AH, Verweij NM, et al. Improved survival for older patients undergoing surgery for colorectal cancer between 2008 and 2011. *Int J Colorectal Dis.* 2014 Oct 15;29(10):1231–6.
19. Verweij NM, Schiphorst AHW, Maas HA, et al. Colorectal Cancer Resections in the Oldest Old Between 2011 and 2012 in The Netherlands. *Ann Surg Oncol.* 2016 Jun 19;23(6):1875–82.
20. Wakahara T, Ueno N, Maeda T, et al. Impact of Gastric Cancer Surgery in Elderly Patients. *Oncology.* 2018;94(2):79–84.
21. Liang Y-X, Deng J-Y, Guo H-H, et al. Characteristics and prognosis of gastric cancer in patients aged ≥ 70 years. *World J Gastroenterol.* 2013;19(39):6568–78.
22. Takeshita H, Ichikawa D, Komatsu S, et al. Surgical outcomes of gastrectomy for elderly patients with gastric cancer. *World J Surg.* 2013;37(12):2891–8.
23. Bartlett EK, Roses RE, Kelz RR, et al. Morbidity and mortality after total gastrectomy for gastric malignancy using the American College of Surgeons National Surgical Quality Improvement Program database. *Surgery.* 2011;156(2):298–304.
24. Nienhueser H, Kunzmann R, Sisis L, et al. Surgery of gastric cancer and esophageal cancer: Does age matter? *J Surg Oncol.* 2015;112(4):387–95.
25. Rice TW, Blackstone EH, Rusch VW. 7th Edition of the AJCC Cancer Staging Manual: Esophagus and Esophagogastric Junction. *Ann Surg Oncol.* 2010;17(7):1721–4.
26. Dindo D, Demartines N, Clavien P-A. Classification of Surgical Complications. *Ann Surg.* 2004 Aug;240(2):205–13.
27. Busweiler LAD, Wijnhoven BPL, van Berge Henegouwen MI, et al. Early outcomes from the Dutch Upper Gastrointestinal Cancer Audit. *Br J Surg.* 2016;103(13):1855–63.
28. Anderson O, Ni Z, Møller H, et al. Hospital volume and survival in oesophagectomy and gastrectomy for cancer. *Eur J Cancer.* 2011;47(16):2408–14.
29. Pisanu A, Montisci A, Piu S, et al. Curative surgery for gastric cancer in the elderly: Treatment decisions, surgical morbidity, mortality, prognosis and quality of life. *Tumori.* 2007;93(5):478–84.
30. Wu CW, Lo SS, Shen KH, et al. Surgical mortality, survival, and quality of life after resection for gastric cancer in the elderly. *World J Surg.* 2000;24(4):465–72.
31. Kim MS, Kim S. Outcome of Gastric Cancer Surgery in Elderly Patients. *J Gastric Cancer.* 2016 Dec;16(4):254–9.
32. Saidi RF, Bell JL, Dudrick PS. Surgical resection for gastric cancer in elderly patients: is there a difference in outcome? *J Surg Res.* 2004 May 1;118(1):15–20.
33. Shimada S, Sawada N, Oae S, et al. Safety and curability of laparoscopic gastrectomy in elderly patients with gastric cancer. *Surg Endosc.* 2018 Mar 30;
34. Dikken JL, Sandick JW Van, Allum WH, et al. Differences in outcomes of oesophageal and gastric cancer surgery across Europe. *Br J Surg.* 2013;100(1):83–94.

CHAPTER NINE

Treating early delayed gastric tube emptying after esophagectomy with pneumatic pyloric dilation

AC Mertens*, JAH Gooszen*, P Fockens, R Voermans, SS Gisbertz, A Bredenoord, MI van Berge Henegouwen

*Both authors contributed equally to this work

Digestive Surgery 2021



ABSTRACT

Introduction

Endoscopic pneumatic pyloric balloon dilation is a treatment option for early postoperative delayed gastric tube emptying following esophageal resection. This study aimed to determine the safety and effectiveness of endoscopic balloon dilation.

Methods

Between 2015-2018 patients with delayed gastric emptying 8-10 days after esophageal resection with gastric tube reconstruction due to esophageal carcinoma were considered for inclusion. Inclusion criteria were ≥ 1 of: nasogastric tube production ≥ 500 ml/24h, ≥ 300 ml gastric retention, $\geq 50\%$ gastric tube dilatation on X-ray or nasogastric tube replacement. Patients were excluded on evidence of anastomotic leakage or reintervention. Success was defined as the ability to expand intake without needing to replace the nasogastric tube. Dilation was performed using a 30mm Rigiflex balloon.

Results

Fifteen patients underwent pyloric dilation, twelve according to the study protocol. Treatment was performed at a median of 12 days (IQR 9-15) postoperatively. Success was achieved in 58%. At 3 months, 8 patients progressed to exclusively oral intake. The remaining 4 patients had supplementary nightly enteral tube feeding. There were no adverse events.

Conclusion

Endoscopic balloon dilation of the pylorus is a safe, feasible therapy for early postoperative delayed gastric emptying. With a success rate of 58%, a clinical trial is a necessary next step.

INTRODUCTION

Delayed gastric emptying affects up to half of patients with a gastric tube reconstruction after an esophagectomy, and can lead to a severely impaired quality of life¹⁻³. Various definitions are used in scientific publications and literature, with an incidence varying between 11-50%³⁻⁷. Delayed gastric emptying can occur early or late, with the cutoff between these commonly set at 3 months after surgery.

A range of treatments exist, with varying success rates. Prophylactic intraoperative treatments like pyloric digital fracture⁸ have shown promising results but could possibly lead to complications. Intraoperative pyloromyotomy or pyloroplasty have shown mixed results and, in our experience, lead to a longer procedure^{9,10}. It is possible to perform pyloric balloon dilation intraoperatively, but this is not extensively researched and warrants an extra endoscopy during the procedure¹¹. Botox injections can be administered intraoperatively, although the results are temporary and this also warrants an intra operative endoscopy¹². Prophylactic interventions can lead to overtreatment since the vast majority of patients will never experience this complication, even without intervention⁴⁻⁶.

Postoperatively, there are a variety of treatment options. Treatment with prokinetic medication such as erythromycin or D2-receptor antagonists like domperidone can be effective but may require continued treatment¹³. Endoscopic treatment with Botox has been proposed as a less invasive (temporary) alternative, but studies show mixed results^{14,15}.

Postoperative endoscopic balloon dilation of the pylorus is increasingly performed and has no reported significant adverse events. However, this is only well described in pre- or intra-operative treatment or in patients treated during outpatient care^{7,16-19}.

This study aimed to evaluate the efficacy and safety of endoscopic pneumatic pyloric balloon dilation in the early postoperative in-hospital phase in patients with delayed gastric emptying after esophagectomy with gastric tube reconstruction.

MATERIALS AND METHODS

This study was conducted in the Amsterdam University Medical Center, location AMC, in Amsterdam. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Review Committee of the Amsterdam University Medical Center (NO.: W16_134 # 16.155) and informed consent requirement was waived for this study.

PATIENT CHARACTERISTICS

To assess the effectiveness of endoscopic pneumatic dilation of the pylorus in the early postoperative phase, all patients 18 years of age or older suffering from early postoperative delayed gastric emptying 8 to 10 days after esophagectomy for cancer with a gastric tube reconstruction without medicinal treatment (eg. motility enhancing medication) were evaluated for inclusion. This timeframe of POD 8-10 was chosen since an earlier intervention might cause an increase risk of anastomotic complications. The definition of early postoperative delayed gastric emptying as used in this study is summarized in Table 1.

Inclusion criteria were nasogastric tube production more than 500ml/24h, gastric retention of more than 300ml as measured by clamping the NGT for three hours, over 50% gastric tube dilatation on AP chest X-ray or the need for replacement of a nasogastric tube at any point after removal.

Patients with an anastomotic leakage, anamnestic evidence of an anastomotic stricture or other surgery-related postoperative morbidity requiring re-intervention or intensive care unit admittance were excluded. Additionally, patients not treated according to the study protocol described in this paper were excluded.

TABLE 1 – DEFINITION OF EARLY DELAYED GASTRIC EMPTYING USED FOR THIS STUDY

ONE OR MORE OF THE FOLLOWING, 8 TO 10 DAYS AFTER THE INITIAL SURGERY:
Inability of removing the nasogastric tube because of persistent production of the nasogastric tube of more than 500ml per 24 hours
Retention of more than 300ml after closure of the nasogastric tube for 4 hours
A > 50% dilatation of the gastric tube on postoperative x-ray, compared with the x-ray directly postoperatively
Replacement of the nasogastric tube (due to nausea, vomiting, thoracic pain or liquid level in gastric tube on chest X-ray)

PROCEDURE

Since patients were included after the esophageal resection, this study did not standardize the surgical technique. All patients received a nasogastric tube and a jejunostomy as standard practice. The different procedures performed in our study cohort are summarized in Table 2. Patients were planned for in-hospital pyloric dilation by one of the available expert interventional endoscopists at the Amsterdam UMC, location AMC, as soon as possible after inclusion. The study protocol is based on our standard practice and was followed in all patients in the cohort. 24 hours prior to the pyloric dilation, patients were kept nil per mouth with suction applied to the nasogastric tube. During dilation, the nasogastric tube was removed. Procedures were performed under conscious or deep sedation. A therapeutic gastroscope was used to identify the pylorus and to exclude an anastomotic stricture. After introduction of a guidewire in the duodenum, the location of the pylorus was identified using fluoroscopy combined with the location of the endoscope. After removing the gastroscope, a 30-millimetre diameter pneumatic balloon (Rigiflex, Boston Scientific®) was introduced over the guidewire until half of the balloon passed the pylorus. The balloon was dilated up to 5psi for one minute, followed by 8psi for another minute.

On the same day as the intervention, patients were started on a clear liquid diet. After this, the diet was expanded to liquid diet, followed by a solid diet according to protocol. On day one and two following the intervention a chest X-ray was made. A nasogastric tube was reinserted in case of more than 50% dilatation of the gastric tube compared to before the procedure, liquid level in the gastric tube or presence of clinical symptoms of nausea, vomiting or thoracic pain. Patients were then placed on clear fluids only. The nasogastric tube was removed when production was less than 300 ml per 24 hours, as measured after clamping the NGT for three hours.

All patients were monitored in the outpatient department following the Dutch guidelines for esophageal cancer, including consultation by a dietician until oral intake was sufficient.

TABLE 2 – CHARACTERISTICS OF PATIENTS INCLUDED IN THE STUDY

Variable		Outcome (N=12)
Age Years, mean (SD)		61 (8.9)
Gender N (%)	Male	10 (83)
ASA Median [IQR]		2 [1-2]
Pre-op BMI Kg/m ² , mean (SD)		25.7 (4.1)
Comorbidities N (%)	Diabetes	0 (-)
	Cardiovascular	7 (58)
	Pulmonary	1 (8)
Neoadjuvant treatment N (%)	Chemotherapy	1 (8)
	Chemoradiotherapy	10 (83)
	None	1 (8)
Tumor type N (%)	Adenocarcinoma	8 (67)
	Squamous cell ca.	3 (25)
	Other	1 (8)
Tumor location N (%)	Mid esophagus	1 (8)
	Distal esophagus	8 (67)
	GE-junction	2 (17)
	Cardia	1 (8)
Reconstruction N (%)	Gastric tube	12 (100)
Conversion N (%)		0 (-)
Surgical approach N (%)	MI Ivor-Lewis	10 (83)
	MI McKeown	1 (8)
	Hybrid Ivor-Lewis	1 (8)
Anastomosis N (%)	Cervical, sutured EtE	1 (8)
	Intrathoracic, stapled EtS	11 (92)
Intraoperative pyloric drainage procedures N (%)		0 (-)
Intraoperative complications N (%)		0 (-)
Postoperative complications N (%)	Pneumonia	1 (8)
	CVA	1 (8)
	Anastomotic leakage	0 (-)
Reason for inclusion N (%)	NGT production	8 (67)
	Over 50% gastric tube distension	4 (33)

Abbreviations: ASA American Society of Anesthesiologists, BMI body mass index, EtE end to end, EtS end to side, GE(J) gastroesophageal junction, IQR interquartile range, LOS length of stay, MI minimally invasive, mm millimeter, SD standard deviation. Percentages may not add up to 100% due to rounding.

TABLE 3 – OUTCOMES OF ENDOSCOPIC PNEUMATIC PYLORIC DILATION IN DELAYED GASTRIC TUBE EMPTYING AFTER ESOPHAGECTOMY

Variable		Outcome (N=12)
PROCEDURE		
Interval from surgery to balloon dilation days, median [IQR]		12 [9-15]
Outcomes after procedure		
Gastric tube dilatation N (%)	<i>Persisting</i>	5 (42)
	<i>Diminishing</i>	5 (42)
	<i>None</i>	1 (8)
	<i>No X-ray performed</i>	1 (8)
Successful treatment N (%)	<i>Clinical</i>	7 (58)
	<i>Technical</i>	12 (100)
Reason for replacement of NGT N (%)	<i>Liquid level in gastric tube</i>	0 (-)
	<i>Gastric tube diameter increase (>50%)</i>	3 (25)
	<i>Nausea, vomiting, pain</i>	2 (17)
	<i>Total</i>	5 (42)
Total length of stay days, median [IQR]		15 [12-16]
Readmission N (%)		1 (8)
90-day mortality N (%)		0 (-)
Hospital stay after intervention days, median [IQR]		4 [2-6]
Diet at day of discharge N (%)	<i>Liquid</i>	6 (50)
	<i>Nil per mouth</i>	3 (25)
	<i>Soft solid</i>	3 (25)
Reflux symptoms N (%)	<i>Yes</i>	4 (33)
LONG-TERM RESULTS		
Diet at 3 months N (%)	<i>Oral</i>	8 (67)
	<i>Oral + enteral tube feeding</i>	4 (33)
	<i>Enteral tube feeding</i>	0 (-)
Diet at 6 months N (%)	<i>Oral</i>	12 (100)
	<i>Oral + enteral tube feeding</i>	0 (-)
Follow-up months, median [IQR]		10 [6-27]
Complete oral diet at last follow-up N (%)	<i>Yes</i>	12 (100)

Abbreviations: IQR interquartile range, NGT nasogastric tube. Percentages may not add up to 100% due to rounding.

OUTCOMES

The primary outcome was clinical treatment success. Clinical treatment success was defined as the ability to expand dietary intake at any rate, without the need to replace the nasogastric tube. Clinical treatment failure was defined as the necessity to replace the nasogastric tube according to the definitions described in the procedure section.

Secondary outcomes were technical success of the pyloric dilatation (the ability to complete the endoscopic pneumatic balloon dilation without complications), dietary intake at discharge, at 3 and 6 months, hospital stay, complication rate, subjective reflux at 6 weeks follow-up, and re-interventions after the pyloric dilation.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS Statistics Version 25.0 (Armonk, NY). Categorical data are presented as absolute numbers and/or percentages. Continuous data are presented as means with standard deviation (SD) for normally distributed data or medians and interquartile ranges (IQR) when not normally distributed.

RESULTS

In the period between November 2015 and October 2018, 239 esophageal resections for cancer with gastric tube reconstruction were performed. Fifteen (6%) patients showed evidence of early postoperative delayed gastric emptying according to the definition in Table 1. All fifteen patients met the inclusion criteria. No patients underwent intraoperative pyloric fracture. Three patients underwent balloon dilation using an 18mm balloon instead of the 30mm balloon described in the study protocol due to preference of the endoscopist and were therefore excluded from further analysis. Table 2 shows the baseline characteristics.

There were no intraoperative complications in any of the patients. Postoperatively one patient suffered from a cerebral vascular infarct directly after surgery requiring intra-arterial thrombectomy with complete recovery. Another patient suffered from pneumonia 3 days postoperatively, successfully treated by antibiotic therapy. The 90-day mortality rate was zero.

PYLORIC BALLOON DILATION

Table 3 outlines the outcomes of early endoscopic pneumatic balloon dilation of the pylorus.

The balloon dilation was clinically successful in seven patients (58%), as defined in the study protocol. Five patients (42%) required replacement of the nasogastric tube: two (17%) due to nausea, vomiting or lateral thoracic pain, and three patients

(25%) due to a more than 50% increase in gastric tube diameter. Following balloon dilation, the median time to discharge was four days (IQR 2-6) with oral intake supplemented with enteral nutrition through the jejunostomy tube in nine patients (75%).

Treatment was a clinical failure in five patients (42%). These five patients spent a median of 2 days before the nasogastric tube could be removed and oral intake was resumed. Three (25%) patients with clinically failed treatment were discharged after removing the nasogastric tube with a nil-per-mouth regimen and enteral tube feeding through a jejunostomy tube. The remaining two (17%) patients with clinically failed treatment were discharged with a nasogastric tube, nil-per-mouth regimen and enteral tube feeding through a jejunostomy tube.

The median total hospital stay was 15 days (IQR 12-16), compared to the median hospital stay of 11 days (IQR 9-17) in the total of 235 patients that underwent an esophagectomy without delayed postoperative gastric emptying in the same period.

At three months after discharge, all twelve patients had oral intake, but in four patients (33%) the total caloric intake was judged as insufficient by the dietician, and supplementary feeding through a jejunostomy tube was needed.

At six months after discharge one patient (8%) had died due to recurrent disease. At six months follow-up there was no clinical evidence of delayed gastric emptying in any of the remaining eleven patients, and all patients had complete oral intake. The median follow-up was 10 months (IQR 6-27).

DISCUSSION

The current study investigated the safety and efficacy of endoscopic pneumatic balloon dilation in the early postoperative in-hospital phase in patients with early postoperative delayed gastric emptying after esophagectomy with gastric tube reconstruction. In our population, we found an incidence of 6%. After pyloric dilation, 58% of patients were able to expand oral intake without replacement of a nasogastric tube. No adverse events occurred.

Various definitions of delayed gastric emptying are used in scientific publications and literature, with an incidence varying between 11 and 50³⁻⁷. The use of different definitions by different authors renders the literature difficult to compare. The low incidence of delayed postoperative gastric emptying in our cohort may be caused by several factors. One reason might be that we only included patients with delayed gastric emptying occurring 8 to 10 days postoperatively. We were interested in this timeframe specifically since an earlier intervention might increase the risk of anastomotic complications. Additionally, the strict definition of this complication combined with a procedure performed before day 11 might have caused a lower incidence than found in the literature. Even though only 6% of our patients fit the criteria of this study, all of these patients had serious complaints. Expanding the inclusion criteria would defeat the purpose of this study.

The literature contains various publications describing uncontrolled series showing promising results for endoscopic balloon dilation^{4,7,18,19}, with success rates varying between 19 and 95%. The best results are seen in patients with postoperative delayed gastric emptying occurring within 3 months postoperatively^{4,17,19}. The current study is the first publication of dilation in the early postoperative period, and our results fall within this wide range. However, where earlier studies¹⁸ reported re-dilation rates of up to 53% at a median of 13 days (range 4-110 days) after the initial dilation, patients in our cohort did not undergo re-dilations.

A possible explanation for the variation in described success rates is the balloon size. An earlier study by Maus et al.¹⁸ has shown that dilation using a 30mm balloon leads to a lower re-dilation rate in postoperative pyloric balloon dilation; 20% after 30mm balloon versus 56% after using a 20mm balloon. The inflation time at maximal pressure (two to three minutes) was longer compared to our cohort (one minute), but there are no clinical studies available comparing inflation times. It is also worth noting that Maus et al. reported that these re-dilations occurred at a median of 13 days (range 4-110 days) after the initial dilation; none of our patients required a re-dilation in this period. One possible explanation for this discrepancy is the longer and vastly wider timeframe of the time to initial dilation in the study; median 19.5 days (range 6–181 days).

Outpatient treatment of delayed gastric conduit emptying is widely utilized; however, outpatient treatment means that patients spend the interval between discharge and the eventual intervention without oral intake, potential enteral tube feeding and a nasogastric tube with accompanying symptoms. One could argue that an initial wait-and-see policy saves a portion of patients from an intervention, allowing for spontaneous resolution of the delayed gastric tube emptying. It is our opinion that the additional waiting period with accompanying symptoms such as loss of appetite, dysphagia, nausea, reflux and regurgitation would call for an earlier intervention.

The current study has several limitations. Most importantly, no control group was used. All patients with early postoperative delayed gastric emptying during the inclusion period have been included in this prospective cohort. Identifying a control cohort in our prospective research database was not possible since data regarding the inclusion criteria (X-ray results, NGT production, etcetera) were not routinely recorded. Including patients from earlier cohorts would lead to bias due to greatly varying treatment protocols. Additionally, one of the conditions for reinserting a nasogastric tube and defining the treatment as a failure was a more aggressive indication of more than 50% increase in diameter of the gastric tube. Due to the nature of a chest X-ray, measuring an increase in diameter is difficult, potentially causing bias. This bias could have led to an overestimation of gastric tube emptying in the four patients that were included based on X-ray characteristics only. Lastly, successful treatment was defined using clinical measures without objective confirmation. It is worth noting that there is no internationally defined standard regarding the normal diameter of a gastric tube reconstruction. In the current study we chose not to include re-dilations in the protocol, in anticipation of the results of this study. In future studies, we will certainly consider re-dilations as a part of the treatment protocol. We believe further studies are indicated, but given the low incidence in the present study as well as the moderate success rate an RCT does not seem feasible.

CONCLUSION

In conclusion, endoscopic pneumatic balloon dilation of the pylorus is a safe and feasible therapy for early postoperative delayed gastric emptying after esophagectomy with a success rate of 58% in this small series. At three months after discharge, all twelve patients had at least partial oral intake.

REFERENCES

- 1 Anandavidvelan P, Wikman A, Johar A, Lagergren P. Impact of weight loss and eating difficulties on health-related quality of life up to 10 years after oesophagectomy for cancer. *British Journal of Surgery*. 2018 Mar;105(4):410–8.
- 2 Deldycke A, Van Daele E, Ceelen W, Van Nieuwenhove Y, Pattyn P. Functional outcome after Ivor Lewis esophagectomy for cancer. *Journal of Surgical Oncology*. 2016 Jan;113(1):24–8.
- 3 Benedix F, Willems T, Kropf S, Schubert D, Stübs P, Wolff S. Risk factors for delayed gastric emptying after esophagectomy. *Langenbeck's Archives of Surgery*. 2017 May;402(3):547–54.
- 4 Li B, Zhang J-H, Wang C, Song T-N, Wang Z-Q, Gou Y-J, et al. Delayed Gastric Emptying After Esophagectomy for Malignancy. *Journal of Laparoendoscopic & Advanced Surgical Techniques*. 2014 May;24(5):306–11.
- 5 Fritz S, Feilhauer K, Schaudt A, Killguss H, Esianu E, Hennig R, et al. Pylorus drainage procedures in thoracoabdominal esophagectomy - A single-center experience and review of the literature. *BMC Surgery*. 2018;18(1):1–8.
- 6 Akkerman RDL, Haverkamp L, van Hillegersberg R, Ruurda JP. Surgical Techniques to Prevent Delayed Gastric Emptying After Esophagectomy With Gastric Interposition: A Systematic Review. *The Annals of Thoracic Surgery*. 2014 Oct;98(4):1512–9.
- 7 Datta J, Williams NN, Conway RG, Dempsey DT, Morris JB. Rescue pyloroplasty for refractory delayed gastric emptying following esophagectomy. *Surgery*. 2014;156:290–7.
- 8 Deng B, Tan Q-Y, Jiang Y-G, Zhao Y-P, Zhou J-H, Chen G-C, et al. Prevention of Early Delayed Gastric Emptying after High-Level Esophagogastrostomy by “Pyloric Digital Fracture.” *World Journal of Surgery*. 2010 Dec;34(12):2837–43.
- 9 Lanuti M, de Delva PE, Wright CD, Gaisert HA, Wain JC, Donahue DM, et al. Post-esophagectomy gastric outlet obstruction: role of pyloromyotomy and management with endoscopic pyloric dilatation. *European Journal of Cardio-thoracic Surgery*. 2007;31(2):149–53.
- 10 Arya S, Markar SR, Karthikesalingam A, Hanna GB. The impact of pyloric drainage on clinical outcome following esophagectomy: A systematic review. *Diseases of the Esophagus*. 2015 May;28(4):326–35.
- 11 Antonoff MB, Puri V, Meyers BF, Baumgartner K, Bell JM, Broderick S, et al. Comparison of Pyloric Intervention Strategies at the Time of Esophagectomy: Is More Better? 2014 DOI: 10.1016/j.athoracsur.2014.02.046
- 12 Tham JC, Nixon M, Ariyathenam A v., Humphreys L, Berrisford R, Wheatley T, et al. Intraoperative pyloric botulinum toxin injection during Ivor-Lewis gastroesophagectomy to prevent delayed gastric emptying. *Diseases of the Esophagus*. 2019 Jun;32(6):1–6.
- 13 Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L. Clinical Guideline: Management of Gastroparesis. *Am J Gastroenterol*. 2013;108(1):18–38.
- 14 Bagheri R, Fattahi SH, Haghi SZ, Aryana K, Aryanniya A, Akhlaghi S, et al. Botulinum toxin for prevention of delayed gastric emptying after esophagectomy. *Asian Cardiovascular and Thoracic Annals*. 2013 Dec;21(6):689–92.

- 15 Eldaif SM, Lee R, Adams KN, Kilgo PD, Gruszynski MA, Force SD, et al. Intrapyloric Botulinum Injection Increases Postoperative Esophagectomy Complications. *The Annals of Thoracic Surgery*. 2014 Jun;97(6):1959–65.
- 16 Kim JH, Lee HS, Kim MS, Lee JM, Kim SK, Zo JI. Balloon dilatation of the pylorus for delayed gastric emptying after esophagectomy. *European Journal of Cardio-thoracic Surgery*. 2008;33(6):1105–11.
- 17 Lanuti M, Dedelva P, Morse CR, Wright CD, Wain JC, Gaissert HA, et al. Management of delayed gastric emptying after esophagectomy with endoscopic balloon dilatation of the pylorus. *Annals of Thoracic Surgery*. 2011 Apr;91(4):1019–24.
- 18 Maus MKH, Leers J, Herbold T, Bludau M, Chon S-H, Kleinert R, et al. Gastric Outlet Obstruction After Esophagectomy: Retrospective Analysis of the Effectiveness and Safety of Postoperative Endoscopic Pyloric Dilatation. *World Journal of Surgery*. 2016 Oct;40(10):2405–11.
- 19 Swanson EW, Swanson SJ, Swanson RS. Endoscopic pyloric balloon dilatation obviates the need for pyloroplasty at esophagectomy. *Surgical Endoscopy*. 2012;26(7):2023–8.

CHAPTER TEN

Transthoracic versus transhiatal esophagectomy for esophageal cancer: a nationwide propensity score-matched cohort analysis

AC Mertens, MC Kalff, WJ Eshuis, TM Van Gulik, MI Van Berge Henegouwen, SS Gisbertz

On behalf of the Dutch Upper GI Cancer Audit group

Annals of Surgical Oncology 2020



ABSTRACT

Background

Chemoradiation followed by resection has been the standard therapy for resectable (cT1-4aN0-3M0) esophageal carcinoma in the Netherlands since 2010. The optimal surgical approach remains a matter of debate. Therefore, the purpose of this study was to compare the transhiatal and the transthoracic approach concerning morbidity, mortality and oncological quality.

Methods

Data was acquired from the Dutch Upper GI Cancer Audit. Patients who underwent esophagectomy with curative intent and gastric tube reconstruction for mid/distal esophageal or esophagogastric junction carcinoma (cT1-4aN0-3M0) from 2011 to 2016 were included. Patients who underwent a transthoracic and transhiatal esophagectomy were compared after propensity score matching.

Results

After propensity score matching, 1532 of 4143 patients were included for analysis. The transthoracic approach yielded more lymph nodes (transthoracic median 19, transhiatal median 14; $p < 0.001$). There was no difference in the number of positive lymph nodes, however, the median (y)pN-stage was higher in the transthoracic group ($p = 0.044$). The transthoracic group experienced more chyle leakage (9.7% vs. 2.7%, $p < 0.001$), more pulmonary complications (35.5% vs. 26.1%, $p < 0.001$), and more cardiac complications (15.4% vs. 10.3%, $p = 0.003$). The transthoracic group required a longer hospital stay (median 14 vs. 11 days, $p < 0.001$), ICU stay (median 3 vs. 1 day, $p < 0.001$), and had a higher 30-day/in-hospital mortality rate (4.0% vs. 1.7%, $p = 0.009$).

Conclusions

In a propensity score-matched cohort, the transthoracic esophagectomy provided a more extensive lymph node dissection, which resulted in a higher lymph node yield, at the cost of increased morbidity and short-term mortality.

INTRODUCTION

As of 2012, esophageal cancer is the eighth most common malignancy worldwide. Both globally and in the Netherlands, a trend of increasing incidence and mortality has been reported.^{1,2} Neoadjuvant chemoradiation (nCRT) following the CROSS regimen with subsequent resection has been the standard treatment for resectable (cT2-4a N0-3 M0 and T0-1 N+ M0) esophageal carcinoma in the Netherlands since 2010.³ While neoadjuvant treatment is fairly standardized in the Netherlands, the optimal surgical approach remains a matter of active debate in both literature and daily practice.

The largest randomized, controlled trial comparing a transthoracic with a transhiatal approach dates back to 2002.^{4,5} It illustrated a trend towards improved survival for patients after a transthoracic resection, in conjunction with a significant 5-year overall survival benefit for the subgroup of patients with 1-8 positive nodes in the resection specimen.^{4,5} However, this trial predates neoadjuvant therapy and is restricted to open procedures, possibly making these results less applicable to current practice. The latest meta-analysis on this subject was published in 2011 and did not find a difference in survival.⁶ It did, however, describe a higher short-term mortality, longer hospital stay, higher lymph node yield, and lower anastomotic leakage rate in the transthoracic group.

Therefore, the purpose of the current study was to compare the transhiatal and transthoracic approach regarding morbidity, mortality, and the quality of the surgical resection for resectable lower esophageal and junction carcinoma in a nationwide cohort study in the Netherlands.

METHODS

Data were obtained from the Dutch Upper GI Cancer Audit (DUCA). This audit was initiated in 2011 and is part of the Dutch Institute for Clinical Auditing (DICA). In the Netherlands, caregivers are obligated to register all patients with esophageal or gastric cancer with intended resection in the DUCA database. The main goal of this audit was to provide transparent information on the

quality of care. Validation of completeness and accuracy of data registration is performed as has been described in earlier publications.⁷ Because the audit data are available anonymously, it is not possible to retrospectively retrieve missing data or include variables, such as surgical procedural

data, hospital of treatment, 90-day mortality, or survival, outside the scope of the audit. This study was approved by the scientific committee of the DUCA. No informed consent or ethical approval was required under Dutch law. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975 and later versions.

PATIENT CHARACTERISTICS AND CLINICAL DATA

All patients undergoing surgery with curative intent for mid to distal esophageal or junction carcinoma (cT1-4aN0-3M0), including cTxNx, from 2011 through 2016 were retrieved from the database. Patients undergoing a three-stage McKeown (cervical anastomosis), a two-stage Ivor Lewis (thoracic anastomosis), or a transhiatal (cervical anastomosis) procedure with gastric tube

reconstruction were included. Patients with missing baseline data and patients undergoing emergency surgery were excluded. Patients undergoing a hybrid resection were excluded due to the heterogeneity of this group; there was no possibility to discern between a laparoscopy combined with a thoracotomy or a laparotomy combined with thoracoscopy.

OUTCOME DATA

The main outcomes were quality-indicators of the surgical resection specimen, including R0 resection rate, circumferential resection margin, and lymph node yield.

Patient, tumor, and treatment characteristics, including perioperative and pathological outcomes, were retrieved from the DUCA database. Complications were defined according to standards of the DUCA. Anastomotic leakage was defined as a clinically or radiologically diagnosed leakage of the esophagus, stomach, anastomosis, or staple line, independent of presentation.

Recurrent nerve lesions were scored without severity, because this was not reported consistently. Short-term oncologic and clinical outcomes were analyzed, including lymph node yield and radicality of resection. Because the DUCA only registers outcomes during the hospital stay and at least the first 30 postoperative days, long-term outcomes were not available for analysis. In-hospital and 30-day mortality are a combined item in the DUCA registration. The Clavien-Dindo classification for complications was only recently added to the audit and omitted from the analysis because of missing data in the earlier years.

STATISTICAL ANALYSIS

The study population was divided into two groups: transthoracic (TTE) and transhiatal (THE) esophagectomy. To minimize the effect of confounders on the outcomes between these groups, a propensity score-matching analysis was performed. A propensity score was calculated for each patient through logistic regression, based on all covariates ($n = 15$) displayed as baseline characteristics in Table 1. Using nearest-neighbor matching without replacement, matched pairs of cases were identified. A caliper of 0.2 was set to prevent poor matches. The balance of the matched cohort was assessed using the standardized mean difference (SMD). A SMD $< 10\%$ was taken to indicate sufficient balance.

The open-source software R 3.5.1 with packages “Matching” version 4.9-3 was used in the propensity score matching process.^{8,9} After assessing balance, the matched cohort was exported for use with SPSS Statistics Version 25.0 (Armonk, NY) for further statistical analysis. Evaluation of differences in outcomes between the two groups after matching was done using paired tests:¹⁰ Paired Student’s t-test for continuous parametric variables, Wilcoxon signed-rank test for nonparametric continuous or ordinal variables and McNemar’s test for nominal variables. Minimally invasive procedures converted to open surgery were analyzed as minimally invasive procedures. All hypothesis tests were two-sided. P values of < 0.05 were considered statistically significant.

TABLE 1: BASELINE DATA COMPARING THE UNMATCHED TO THE PROPENSITY MATCHED COHORT, WITH SUBDIVISION BETWEEN TRANSTHORACIC AND TRANSHIATAL APPROACH

	UNMATCHED COHORT				AFTER PROPENSITY SCORE MATCHING				
	TTE (N = 2409)		THE (N = 1198)		TTE (N = 766)		THE (N = 766)		
	n	%	n	%	n	%	n	%	
Sex									SMD
Female	555	23.0	243	20.3	145	18.9	154	20.1	0.030
Male	1854	77.0	955	79.7	621	81.1	612	79.9	
Age									
median	65	[59-70]	66	[60-72]	66	[21-71]	66	[60-72]	0.026
BMI									
median	25	[23-28]	26	[23-29]	26	[23-28]	26	[23-29]	0.003
ASA-score									
I	419	17.4	192	16.0	122	15.9	120	15.7	0.065
II	1506	62.5	694	57.9	445	58.1	462	60.3	
III	478	19.8	303	25.3	196	25.6	179	23.4	
IV	6	0.2	9	0.8	3	0.4	5	0.7	
Comorbidities									
Pulmonary	421	17.5	242	20.2	143	18.7	148	19.3	0.017
Cardiac	528	21.9	312	26.0	190	24.8	195	25.5	0.015
Vascular	866	35.9	508	42.4	295	38.5	308	40.2	0.035
Diabetes	332	13.8	219	18.3	138	18.0	133	17.4	0.017
Histology									
AC	1841	76.4	1055	88.1	651	85.0	651	85.0	0.001
SCC	568	23.6	143	11.9	115	15.0	115	15.0	
cT stage									
Tis	3	0.1	1	0.1	2	0.3	1	0.1	0.057
T1	122	5.1	58	4.8	48	6.3	43	5.6	
T2	439	18.2	234	19.5	140	18.3	141	18.4	
T3	1684	69.9	828	69.1	517	67.5	529	69.1	
T4	71	2.9	32	2.7	26	3.4	22	2.9	
Tx	90	3.7	45	3.8	33	4.3	30	3.9	

cN stage	N0	818	34.0	445	37.1	0.113	265	34.6	292	38.1	0.100
	N1	988	41.0	473	39.5		300	39.2	288	37.6	
	N2	448	18.6	201	16.8		143	18.7	141	18.4	
	N3	74	3.1	26	2.2		20	2.6	18	2.3	
	N+	25	1.0	12	1.0		9	1.2	8	1.0	
	Nx	56	2.3	41	3.4		29	3.8	19	2.5	
Location of tumor	Middle	410	17.0	31	2.6	0.644	28	3.7	31	4.0	0.029
	Distal	1598	66.3	721	60.2		521	68.0	512	66.8	
	GEJ	401	16.6	446	37.2		217	28.3	223	29.1	
Neoadjuvant	None	163	6.8	124	10.4	0.190	78	10.2	81	10.6	0.044
	Chemother.	130	5.4	103	8.6		66	8.6	57	7.4	
treatment	CRT	2115	87.8	971	81.1		622	81.2	628	82.0	
Year of surgery	2011	226	9.4	271	22.6	0.508	120	15.7	122	15.9	0.038
	2012	348	14.4	231	19.3		142	18.5	135	17.6	
	2013	348	14.4	195	16.3		123	16.1	125	16.3	
	2014	439	18.2	198	16.5		138	18.0	144	18.8	
	2015	524	21.8	189	15.8		136	17.8	139	18.1	
	2016	524	21.8	114	9.5		107	14.0	101	13.2	
Type of surgery	MIS	1836	76.2	323	27.0	1.110	321	41.9	323	42.2	0.005
	Open	573	23.8	866	72.3		445	58.1	443	57.8	

Percentages might not add up to 100% due to rounding. Numbers between brackets depict the interquartile range. AC adenocarcinoma; ASA American Society of Anesthesiologists; BMI body mass index; cT clinical T stage; cN clinical N stage; CRT chemoradiotherapy; GEJ gastroesophageal junction; MIS minimally invasive surgery; SCC squamous cell carcinoma; SMD standardized mean difference; TTE transthoracic esophagectomy; THE transhiatal esophagectomy

TABLE 2: SURGICAL AND HISTOPATHOLOGICAL OUTCOMES, SHOWING BOTH THE UNMATCHED AND THE PROPENSITY MATCHED COHORT, WITH COMPARISON BETWEEN TRANSTHORACIC AND TRANSHIATAL APPROACH

	UNMATCHED COHORT						AFTER PROPENSITY SCORE MATCHING					
	TTE (N = 2409)			THE (N = 1198)			TTE (N = 766)			THE (N = 766)		
	N	%	P	N	%	P	N	%	P	N	%	P
Anastomosis												
Cervical	1218	50.6		1198	100.0	<0.001	376	49.1		766	100.0	<0.001
Intrathoracic	1191	49.4		-	-		390	50.9		0	0.0	
Conversion*												
None	1727	71.7		297	24.8	<0.001	302	39.4		288	37.6	0.728
Early	18	0.7		7	0.6		4	0.5		7	0.9	
Late	43	1.8		10	0.8		6	0.8		10	1.3	
NA (open)	573	23.8		866	72.3		445	58.1		443	57.8	
Resection												
R0	2266	94.1		1116	93.2	0.012	719	93.9		717	93.6	0.109
R1	115	4.8		65	5.4		44	5.7		39	5.1	
R2	0	0.0		4	0.3		0	0.0		2	0.3	
CRM median, mm	3	[1-7]		2.5	[1-6]	0.004	3	[1-6]		3	[2-7]	0.549
Lymph nodes, median												
Number	20	[15-27]		14	[10-19]	<0.001	19	[15-26]		14	[10-19]	<0.001
Positive	0	[0-1]		0	[0-2]	0.560	0	[0-2]		0	[0-2]	0.375
Ratio	0	[0-0.07]		0	[0-0.13]	0.030	0	[0-0.09]		0	[0-0.12]	0.122
(y) pT stage												
T0	553	23.0		256	21.4	0.038	150	19.6		164	21.4	0.404
Tis	18	0.7		15	1.3		8	1.0		10	1.3	
T1	416	17.3		169	14.1		123	16.1		116	15.1	
T2	432	17.9		245	20.5		131	17.1		154	20.1	
T3	850	35.3		448	37.4		311	40.6		280	36.6	
T4	6	0.2		4	0.3		5	0.7		8	1.0	
Tx	11	0.5		10	0.8		38	5.0		34	4.4	

(y)pN stage	N0	1380	57.3	713	59.5	0.165	426	55.6	461	60.2	0.044
	N1	516	21.4	221	18.4		172	22.5	151	19.7	
	N2	262	10.9	144	12.0		87	11.4	79	10.3	
	N3	138	5.7	67	5.6		46	6.0	41	5.4	
	Nx	2	0.1	6	0.5		35	4.6	34	4.4	
(y)pM stage	M0	2300	95.5	1164	97.2	0.374	729	95.2	739	96.5	0.557
	M1	22	0.9	15	1.3		7	0.9	12	1.6	
	Mx	54	2.2	6	0.5		30	3.9	15	2.0	
Response to	None	214	8.9	85	7.1	<0.001	73	9.5	47	6.1	0.073
neoadjuvant treatment	Partial	1267	52.6	632	52.8		390	50.9	405	52.9	
	Complete	659	27.4	307	25.6		190	24.8	204	26.6	

Percentages might not add up to 100% due to rounding. Numbers between brackets depict the interquartile range. mm millimeters; NA not applicable; TTE transthoracic esophagectomy; THE transhiatal esophagectomy; (y)pT pathological T stage; (y)pN pathological N stage; (y)pM pathological M stage.

*Early conversion: 30 min of incision, late conversion: 30 min of incision

RESULTS

STUDY POPULATION

From 2011 through 2016, 4143 patients underwent an esophagectomy with curative intent in the Netherlands. In total, 536 (13%) patients were excluded from further analysis due to nonelective surgery ($n = 13$), cervical esophageal carcinoma ($n = 44$), reconstruction other than gastric tube ($n = 64$), hybrid surgery ($n = 114$), or missing preoperative data ($n = 301$).

Patients were divided into two groups based on the operative approach: transthoracic (TTE) or transhiatal (THE) esophagectomy. As depicted in Table 1, 11 of 15 baseline characteristics were unequally distributed between the groups in the unmatched cohort ($SMD > 0.10$). Through propensity score matching, 766 patients were matched in each group. The matched cohort was well balanced.

SURGICAL AND HISTOPATHOLOGICAL OUTCOMES

Surgical and histopathological outcomes are shown in Table 2. In the propensity score matched cohort, the transthoracic approach yielded more lymph nodes (TTE median 19, interquartile range [IQR] 15–26; THE median 14, IQR 10–19; $p < 0.001$), but there was no difference in the median number of positive lymph nodes. Additionally, the TTE group had a higher (y)pN stage, even though the groups were matched on cN stage. The (y)pT stage, (y)pM stage, and the response to neoadjuvant therapy were distributed equally between groups. R0 resection was achieved in 94% of cases (TTE 93.9%, THE 93.6%). Due to the nature of the two surgical procedures, all patients in the THE group had a cervical anastomosis, whereas the TTE group contained both cervical and intrathoracic anastomoses. The distribution of the anastomotic location was comparable to the unmatched cohort.

POSTOPERATIVE OUTCOMES

Table 3 depicts the postoperative outcomes. After propensity score matching, no statistically significant differences remained in morbidity (62.9% vs. 58.2%, $p = 0.054$) and infections ($p = 0.099$). The TTE group less often received tube feeding (86.2% vs. 93.0%, $p < 0.001$), experienced more chyle leakages (9.7% vs. 2.7%, $p < 0.001$), more pulmonary complications (35.5% vs. 26.1%, $p < 0.001$), and more cardiac complications (15.4% vs. 10.3%, $p = 0.003$). In addition to this, the TTE group had a longer hospital stay (median 14 vs. 11 days, $p < 0.001$), longer ICU stay (median 3 vs. 1 day, $p < 0.001$), and had a higher in-hospital/30-day mortality (4.0% vs. 1.7%, $p = 0.009$).

DISCUSSION

This study investigated the short-term outcomes of transthoracic and transhiatal esophagectomy for cancer in a nationwide propensity score matched analysis. The results show that a transthoracic approach provides a more thorough oncologic resection with a higher lymph node yield, at the cost of increased morbidity and short-term mortality. This is a population-based study, with all the variations in treatment this entails, giving a reflection of actual daily practice in the Netherlands. By utilizing a national database, we were able to study a much larger group of patients than would have otherwise been possible through a randomized, controlled trial. Furthermore, the present study reflects the results of the surgical treatment of esophageal cancer on a nationwide level compared with various publications, including only results from specialized tertiary centers. Our analysis therefore resembles real-world results more closely. However, this resemblance results in discrepancies compared with the guidelines: some patients with a mid-esophageal carcinoma were treated by THE, while the national guideline advises a transthoracic approach. Because this study also includes patients from smaller low-volume centers, the outcomes from our analysis also show, for example, higher anastomotic leakage and mortality rates and a lower lymph node yield compared with studies that only report outcomes of a single, specialized center or exclusively of high-volume (tertiary) centers.

The inclusion period of this study starts in 2011, which was the year of initiation of the DUCA. We know from earlier research that surgical care for esophageal cancer in the Netherlands has significantly evolved since 2011. The two largest changes in our country during the inclusion period of this study were the introduction of centralization of care with a minimum yearly hospital case-volume of 20 cases per year⁷ and the introduction of minimally invasive procedures¹¹. The process of implementing the minimum volume per hospital is still in progress. In the Netherlands in 2016, 22 hospitals performed esophagectomies for esophageal cancer.¹²

Five of these performed less than 20 resections in that year, three performed 20–29 resections, five performed 30–39 resections, and the remaining nine performed 40 or more resections in that year. This means that in 2016, five hospitals did not meet the minimum volume set in the national guidelines. The number of cases per surgeon is not recorded in the audit. Through the matching process we aimed to correct this potential bias by including the surgical approach and year of surgery as covariates. This means that at the start of the cohort, most minimally invasive procedures could not be matched due to the smaller volume of minimally invasive procedures, whereas in the more recent years of the cohort, many open esophagectomies could not be matched due to the smaller volume of open resections.

TABLE 3: POSTOPERATIVE OUTCOMES, SHOWING BOTH THE UNMATCHED AND THE PROPENSITY-MATCHED COHORT, WITH COMPARISON BETWEEN TRANSTHORACIC AND TRANSHIATAL APPROACH

	UNMATCHED COHORT						AFTER PROPENSITY SCORE MATCHING					
	TTE (N = 2409)			THE (N = 1198)			TTE (N = 766)			THE (N = 766)		
	N	%	P	N	%	P	N	%	P	N	%	P
Intraoperative complications	116	4.8	59	4.9	0.870	45	5.9	36	4.7	0.368		
Tube feeding	2120	88.0	1099	91.7	0.001	660	86.2	712	93.0	<0.001		
Type of tube feeding	2006	83.3	1001	83.6	0.002	622	81.2	651	85.0	0.310		
<i>Jejunostomy</i>												
<i>NJT</i>	48	2.0	46	3.8	18	2.3	27	3.5				
Postoperative complications	1482	61.5	660	55.1	0.000	482	62.9	446	58.2	0.054		
<i>Any</i>												
<i>Tromboembolic</i>	54	2.2	22	1.8	0.437	23	3.0	12	1.6	0.059		
<i>Neurologic/psychiatric</i>	230	9.5	132	11.0	0.152	77	10.1	88	11.5	0.413		
<i>Infectious</i>	116	4.8	91	7.6	0.001	47	6.1	66	8.6	0.099		
<i>Chyle leak</i>	246	10.2	28	2.3	<0.001	74	9.7	21	2.7	<0.001		
<i>Gastro-intestinal</i>	550	22.8	259	21.6	0.483	157	20.5	173	22.6	0.290		
<i>Urological</i>	73	3.0	35	2.9	0.876	24	3.1	20	2.6	0.635		
<i>Pulmonary</i>	805	33.4	292	24.4	<0.001	272	35.5	200	26.1	<0.001		
<i>Cardiac</i>	354	14.7	130	10.9	0.002	118	15.4	79	10.3	0.003		
<i>Anastomotic leakage</i>	466	19.3	220	18.4	0.287	140	18.3	149	19.5	0.606		
<i>Recurrent nerve lesion</i>	109	4.5	67	5.6	0.163	30	3.9	45	5.9	0.092		

Reintervention	Any	639	26.5	117	9.8	<0.001	194	25.3	110	14.4	<0.001
	Under GA	99	4.1	28	2.3	0.002	19	2.5	21	2.7	0.868
	Radiological	248	10.3	63	5.3	<0.001	81	10.6	43	5.6	0.001
	Endoscopic	257	10.7	38	3.2	<0.001	63	8.2	26	3.4	<0.001
	Surgical	370	15.4	115	9.6	<0.001	113	14.8	71	9.3	0.002
ICU stay, median, days		2	[1-5]	1	[1-4]	<0.001	3	[1-6]	1	[1-3]	<0.001
LOS, median, days		13	[9-21]	11	[9-16]	<0.001	14	[10-23]	11	[9-16]	<0.001
Readmittance		364	15.1	131	10.9	0.001	103	13.4	85	11.1	0.192
30-day/in-hospital mortality		88	3.7	30	2.5	0.082	31	4.0	13	1.7	0.009

Percentages might not add up to 100% due to rounding. Numbers between brackets depict the interquartile range. GA general anesthesia; ICU intensive care unit; IQR interquartile range; LOS length of stay; MIS minimally invasive surgery; NA not applicable; NJT nasogastric tube

TTE provided a superior lymph node yield over THE, accompanied by a higher (y) pN stage compared with patients who underwent a THE. The results also show that 50% of the transhiatal resections had a lymph node yield lower than 14. In the case of a transthoracic resection, only 25% of patients had a lymph node yield below the national guideline of 15. Even though the number of positive nodes was equal in both groups, the question arises whether positive nodes have been missed in the lymph node dissection during transhiatal surgery. Because the cN stage was comparable between groups, although borderline matched (SMD 0.100), a selection bias causing patients with a higher cN to be more likely to undergo a TTE seems an unlikely explanation. The surgical community is divided on the value of an extended lymph node dissection after neoadjuvant chemoradiation.

Noordman et al. concluded from their study with the CROSS cohort, that nCRT for esophageal adenocarcinomas might reduce the need for an extended lymphadenectomy, as can be performed with a transthoracic resection.¹³ A transthoracic resection was independently associated with a more favorable prognosis in the surgery alone group, whereas a TTE with additional nCRT was not. In addition to this, Kurokawa et al. prospectively investigated the distribution of lymph node metastases in gastroesophageal junction tumors, and found that a limited lymph node resection could be sufficient in patients with tumors involving less than 4 centimeters of the esophagus.¹⁴ Another study investigating whether a subgroup of patients could benefit from conservative management following neoadjuvant therapy is currently ongoing in the Netherlands.¹⁵ On the contrary, a recent study found an association between an extensive lymph node dissection during esophagectomy and prolonged survival.⁴ Furthermore, a recent study by Raja et al. on post-neoadjuvant esophageal resection found that resecting up to 25 lymph nodes in ypN0 tumors or resecting up to 30 lymph nodes in ypN0 tumors resulted in increased survival.¹⁶ The presence of positive nodes after nCRT has been associated with survival, which makes lymph node dissection essential for determining the prognosis.¹⁷ Additionally, TTE has been linked to a higher 5-year survival compared with THE in the case of positive nodes in the resection specimen, making the risk of potentially missed positive nodes after THE even more relevant.⁵

Our analysis showed that patients treated by a transthoracic esophagectomy experienced more chyle leakages, pulmonary, and cardiac complications. Additionally, they needed more reinterventions and had a longer ICU and hospital stay. The number of recurrent nerve lesions of any severity was comparable between TTE versus THE. The THE group received tube feeding more frequently, also after propensity score matching. This difference could be explained by differences in treatment protocols between hospitals. Unfortunately, information on hospital of treatment and treatment protocol is lacking in the DUCA database, so this theory

cannot be confirmed by data in this study. The short-term mortality (in-hospital/30-day mortality) was significantly higher in the transthoracic group. The authors suspect that despite a comparable anastomotic leakage rate, the lower mortality in the THE group may be explained by less severe manifestations of leakage. As a result of reduced surgical pleural dissection, especially in the upper mediastinum, any leakage will likely result in limited mediastinal manifestations. This hypothesis is supported by earlier research showing a reduced incidence of intrathoracic complications of anastomotic leakage after a THE (27%) compared with a TTE with cervical anastomosis (44%) with similar incidence of anastomotic leakage between groups.¹⁸

Many publications regarding this subject suffer from bias since patients undergoing a THE generally differ significantly from those undergoing a TTE. Although some centers prefer one of these approaches for all their patients, most studies show evidence of selective allocation to the procedures based on preoperative condition, comorbidities of the patient, and cTNM staging. The current study shows that the known increased morbidity and mortality after a transthoracic approach for esophagectomy can be expected even in patients matched on baseline characteristics. A randomized trial comparing total gastrectomy via an abdominal-transhiatal approach versus a left thoracoabdominal approach found similar results as were found in this study: more complications in the group with the extended approach.¹⁹ In addition, survival did not improve with the more aggressive approach in this randomized, controlled trial. Results however, cannot directly be extrapolated to the patients in this study, because this randomized, controlled trial compares gastrectomy for cardia and subcardia cancer and not esophagectomy for esophageal and gastroesophageal junction cancer.

The generalization of our results is reduced by the fact that we excluded hybrid procedures and nongastric-tube reconstructions after esophagectomy. Performing a subgroup analysis after propensity score matching is statistically unfeasible.²⁰ We have explored the possibility of a 3-arm propensity score matching analysis (TTE with intrathoracic anastomosis, TTE with cervical anastomosis, and THE). However, because propensity score matching discarded nonmatched subjects, this led to very small groups no longer representative of the original cohort. In addition, because only the transthoracic group could be divided in an intrathoracic and cervical anastomosis group, correcting for this confounder was not possible. Because the audit does not disclose the hospital of origin of patients, we were unable to compare the two groups regarding the relation between hospital volume and complications, mortality, and pathology outcome. Because the results of this study may be influenced by the results of individual hospitals or by hospital volume, this is a limitation of the current study. In addition, evaluation of large cohorts of

patients could lead to an inherent selection bias: the choice of the surgery type can be made based on experience, principle but also by necessity. Apart from this possible selection bias, propensity score matching does not correct for unknown confounders, and as such residual bias may be present. As stated in the Methods section, DUCA only registers outcomes during the first 30 postoperative days. Because of this, long-term outcomes are not available for analysis. Data regarding lymph node yield per region was only recently added to the audit, and subject to change, and therefore not included. Additionally, we do not have any information on location of suspicious lymph nodes, which could have led to a TTE for oncologic reasons, nor on information regarding surgical preference. Survival data are not part of the DUCA registration: this would have increased the value of the mortality analysis. The current study is nonetheless of great value because of the large number of patients included and correction for the often-reported selection bias through propensity score matching on baseline characteristics.

CONCLUSIONS

Our analysis showed that, even after correction for baseline characteristics, a transthoracic approach provides a higher lymph node yield, at the cost of increased morbidity and short-term mortality. The lower lymph node yield after a transhiatal resection could indicate positive lymph nodes left in situ. Although results in high-volume centers and RCTs often are superior, these data reflect the national performance. We believe future research should investigate further whether long-term survival differs between a transthoracic and transhiatal resection in the era of (neo)adjuvant therapy, minimally invasive surgery, and increasingly centralized care.

REFERENCES

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin.* 2015 Mar;65(2):87–108.
2. IKNL. Nederlandse Kankerregistratie (NKR). [cited 2018 Nov 20]. Available from: <https://www.cijfersoverkanker.nl>
3. Van Hagen P, Hulshof MCCM, Van Lanschot JJB, et al. Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer. *N Engl J Med.* 2012;366(22):2074–84.
4. Hulscher JBF, Van Sandick JW, De Boer AGEM, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. *N Engl J Med.* 2002;347(21):1662–9.
5. Omloo JMT, Lagarde SM, Hulscher JBF, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. *Ann Surg.* 2007 Dec;246(6):992–1000; discussion 1000-1.
6. Boshier PR, Anderson O, Hanna GB. Transthoracic versus transhiatal esophagectomy for the treatment of esophagogastric cancer: A meta-analysis. *Ann Surg.* 2011;254(6):894–906.
7. Busweiler LAD, Wijnhoven BPL, van Berge Henegouwen MI, et al. Early outcomes from the Dutch Upper Gastrointestinal Cancer Audit. *Br J Surg.* 2016;103(13):1855–63.
8. R Core Team (2013). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria.;
9. Sekhon JS. Multivariate and Propensity Score Matching Software with Automated Balance Optimization: The Matching Package for R. *J Stat Softw.* 2011;
10. Austin PC. Comparing paired vs non-paired statistical methods of analyses when making inferences about absolute risk reductions in propensity-score matched samples. *Stat Med.* 2011 May 20;30(11):1292–301.
11. Seesing MFJ, Gisbertz SS, Goense L, et al. A Propensity Score Matched Analysis of Open Versus Minimally Invasive Transthoracic Esophagectomy in the Netherlands. *Ann Surg.* 2017 Nov;266(5):1.
12. DICA. Toegenomen aantal maag- en slokdarmresecties per ziekenhuis (Increased number of gastric and esophageal resections per hospital). 2017 [cited 2020 Mar 22]. Available from: <https://dica.nl/nieuws/duca-juni>
13. Noordman BJ, van Klaveren D, van Berge Henegouwen MI, et al. Impact of Surgical Approach on Long-term Survival in Esophageal Adenocarcinoma Patients With or Without Neoadjuvant Chemoradiotherapy. *Ann Surg.* 2018;267(5):892–7.
14. Kurokawa Y, Takeuchi H, Doki Y, et al. Mapping of Lymph Node Metastasis From Esophagogastric Junction Tumors. *Ann Surg.* 2019;XX(Xx):1.
15. Noordman BJ, Wijnhoven BPL, Lagarde SM, et al. Neoadjuvant chemoradiotherapy plus surgery versus active surveillance for oesophageal cancer: A stepped-wedge cluster randomised trial. *BMC Cancer.* 2018;18(1).
16. Hulscher JBF, Van Sandick JW, De Boer AGEM, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. *N Engl J Med.* 2002;347(21):1662–9.

17. Raja S, Rice TW, Murthy SC, et al. Value of Lymphadenectomy in Patients Receiving Neoadjuvant Therapy for Esophageal Adenocarcinoma. *Ann Surg.* 2019 Dec;1.
18. Talsma AK, Shapiro J, Looman CWN, et al. Lymph node retrieval during esophagectomy with and without neoadjuvant chemoradiotherapy: Prognostic and therapeutic impact on survival. *Ann Surg.* 2014;260(5):786–93.
19. Van Heijl M, Van Wijngaarden AKS, Lagarde SM, et al. Intrathoracic manifestations of cervical anastomotic leaks after transhiatal and transthoracic oesophagectomy. *Br J Surg.* 2010;97(5):726–31.
20. Sasako M, Sano T, Yamamoto S, et al. Left thoracoabdominal approach versus abdominal-transhiatal approach for gastric cancer of the cardia or subcardia: a randomised controlled trial. *Lancet Oncol.* 2006 Aug;7(8):644–51.
21. Wang S V., Jin Y, Fireman B, et al. Relative performance of propensity score matching strategies for subgroup analyses. *Am J Epidemiol.* 2018;187(8):1799–807.

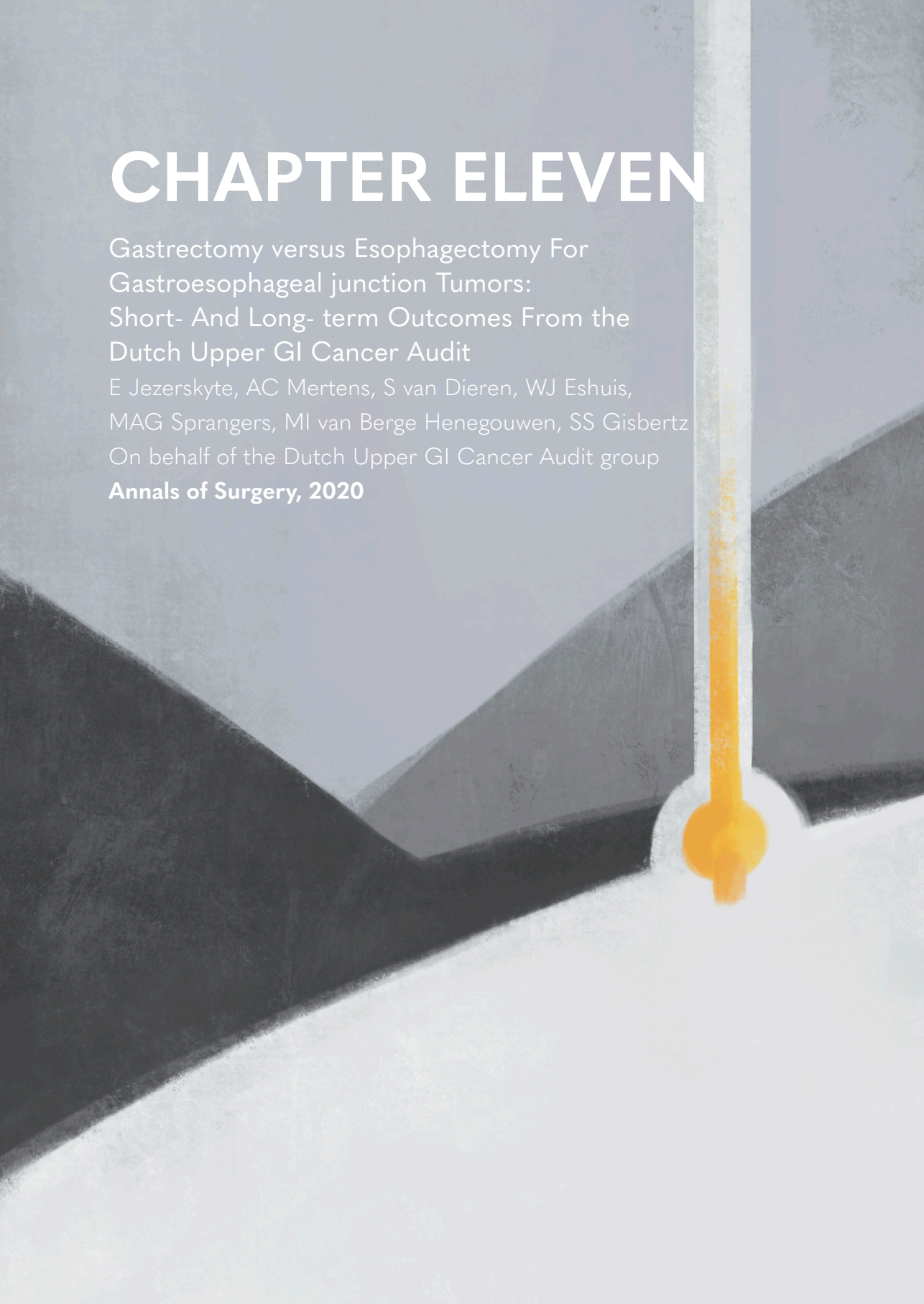
CHAPTER ELEVEN

Gastrectomy versus Esophagectomy For
Gastroesophageal junction Tumors:
Short- And Long- term Outcomes From the
Dutch Upper GI Cancer Audit

E Jezerskyte, AC Mertens, S van Dieren, WJ Eshuis,
MAG Sprangers, MI van Berge Henegouwen, SS Gisbertz

On behalf of the Dutch Upper GI Cancer Audit group

Annals of Surgery, 2020



ABSTRACT

Objective

Investigate long-term survival, morbidity, mortality and pathology results in patients following esophagectomy or total gastrectomy for GEJ cancer.

Background

Both a total gastrectomy and an esophagectomy may be valid treatment options in patients with gastroesophageal junction (GEJ) cancer. Which procedure results in the most optimal patient outcome is not well studied. The aim of this study was to investigate the long-term survival, morbidity, mortality and pathology results in patients following esophagectomy or total gastrectomy for GEJ cancer.

Methods

A retrospective comparative cohort study of prospectively collected data from the Dutch Upper GI Cancer Audit combined with survival data of the Dutch medical insurance database was performed. Patients with GEJ cancer in whom a total gastrectomy or an esophagectomy was performed between 2011-2016 were compared. The primary outcome was 3-year overall survival. Postoperative morbidity, mortality, 3-year conditional survival, radicality of resection and lymph node yield were secondary endpoints.

Results

A total of 871 patients were included: 790 following esophagectomy and 81 following gastrectomy. The 3-year overall survival was 35.8% after esophagectomy and 28.4% after gastrectomy (HR 1.2, 95%CI 0.721-1.836, $p=0.557$). Postoperative morbidity, mortality, radicality of resection, lymph node yield and 3-year conditional survival did not differ significantly between groups.

Conclusion

A total gastrectomy and an esophagectomy for GEJ cancer show largely comparable results with regard to long-term survival, postoperative morbidity, mortality and pathology results. If both procedures are feasible other parameters such as surgeon's experience and quality of life should be considered when planning for surgery.

INTRODUCTION

Cancer of the gastroesophageal junction (GEJ) has a rapidly increasing incidence¹. Treatment usually consists of (neo)adjuvant chemo(radio)therapy and surgery². Both a total gastrectomy and an esophagectomy may be technically possible and selecting the most suitable surgical procedure poses a challenge to surgeons treating GEJ cancer. There is no conclusive evidence which procedure yields the best outcome regarding postoperative morbidity and mortality, pathology results (radicality of surgery and lymph node yield) and long-term survival.

As esophagectomy usually includes a thoracic part, which induces more surgical trauma and, especially if an open esophagectomy is performed, is associated with an increased incidence of pulmonary complications^{3,4}. However, a more extensive lymphadenectomy can be performed during a thoracoabdominal approach, compared to an abdominal approach⁵. Furthermore, a lower rate of R1 resections may be found following a transthoracic approach (esophagectomy) compared to a transhiatal approach (gastrectomy)^{6,7}. Two recent systematic reviews reported no difference in 5-year survival, 30-day mortality and pathology results between esophagectomy and gastrectomy^{8,9} although one of those systematic review⁸ reported a higher rate of postoperative morbidity after an esophagectomy compared to a gastrectomy. Even though the 30-day mortality is described in most studies included in these systematic reviews, the long-term survival rate is poorly investigated. Also, heterogeneity exists in and between the included studies, as some included not only GEJ but also distal esophageal and gastric cardia cancer, and some excluded patients following neoadjuvant therapy, making results difficult to interpret for patients with true GEJ cancer in the era of neoadjuvant therapy.

The aim of this study was to investigate the difference in long-term survival, postoperative morbidity, mortality and pathology results in GEJ cancer patients following an esophagectomy or a total gastrectomy at a population level. We hypothesized to find a higher 3-year overall and conditional survival in the esophagectomy group, because a more extended lymphadenectomy can be performed with a lower chance of a proximal non-radical resection, however, at the cost of increased postoperative morbidity.

METHODS

STUDY DESIGN AND PATIENT POPULATION

The data for this population-based comparative cohort study was obtained from the Dutch Upper Gastrointestinal Cancer Audit (DUCA)¹⁰. The DUCA is a mandatory national audit, containing prospective data on the diagnostic process and surgical results of all patients with esophageal or gastric cancer operated in the Netherlands. The purpose of this registration is to gain insight into the quality of care and to accelerate its improvement. This system points to potential areas for improvement as hospitals receive feedback on their own results, compared to the national average. Patients in the DUCA are operated by gastro-intestinal surgeons, who perform both the thoracic as well as the abdominal part of an esophagectomy. The same surgeons usually also perform the gastrectomies (although in few centers only esophagectomies or only gastrectomies are being performed). Survival data was obtained from VEKTIS, a database of medical insurance organizations of the Netherlands, containing the date of death and information on medical treatments of almost all Dutch people (99%)¹¹. Survival data from the VEKTIS database was merged with the DUCA database on the 1st of September, 2017 and the validation of accuracy and completeness has been previously described in a separate article by van der Werf et al.¹².

Surgeons who registered patients in the DUCA database, could choose from ten input options for tumor location: cervical, intrathoracic (proximal part), intrathoracic (middle part), intrathoracic (distal part), esophagus-stomach transition point (GEJ), fundus, corpus, antrum, pylorus and diffuse gastric cancer. Choice for location was made by the responsible surgeon. Patients with an adenocarcinoma of the GEJ were included in this study. Patients who underwent a total gastrectomy or an esophagectomy (transthoracic and transhiatal) with curative intent in the period between January 2011 and December 2016 were compared. Patients in whom no anastomosis was performed or who underwent no resection, patients operated for recurrent disease, or patients with a colonic or jejunal interposition, patients undergoing salvage, palliative or emergency surgery, and patients with a squamous cell carcinoma were excluded from this study. In addition, all patients who underwent a subtotal gastrectomy were excluded. In the Netherlands, a subtotal gastrectomy is a distal gastrectomy, hence cannot be performed for a GEJ cancer. Ethical approval for this study was not required under Dutch law. The STROBE checklist was used for guidance during the composition of this paper¹³.

(NEO)ADJUVANT THERAPY

(Neo)adjuvant therapy was administered according to the Dutch guidelines for gastric and esophageal cancer^{14,15}. In case of a true GEJ cancer, patients usually received neoadjuvant chemoradiotherapy according to the CROSS regimen¹⁶. Patients with

cardia or GEJ cancers extending >2cm in to the stomach were usually treated with perioperative chemotherapy (EOX: Epirubicin, Oxaliplatin and Capecitabine) according to MAGIC study protocol¹⁷. Patients who participated in the CRITICS study received adjuvant chemoradiotherapy following neoadjuvant chemotherapy and gastrectomy¹⁸. Patients with World Health Organization functional Classification (WHO) grade ≥ 3 or early stage cancer (\leq cT2N0) received no neoadjuvant or perioperative therapy¹⁹.

SURGICAL TECHNIQUES

Surgery was performed according to the Dutch guidelines for gastric and esophageal cancer^{14,15}. In total gastrectomy, the entire stomach was removed by a minimally invasive or an open approach with a modified D2 lymphadenectomy, after which an esophagojejunostomy was created with Roux-Y reconstruction. An esophagectomy was either performed open or minimally invasively by a transthoracic (TTE) or transhiatal (THE) approach, with an extended 1-field (THE) or 2-field (TTE) lymphadenectomy, with a cervical or intrathoracic esophagogastric anastomosis.

ENDPOINTS

The primary endpoint was 3-year overall survival. Long-term disease specific survival could not be analyzed as the cause of death was not registered in either the VEKTIS or DUCA database. Secondary endpoints were postoperative morbidity (anastomotic dehiscence, pulmonary complications, chyle leakage, cardiac complications, supraventricular arrhythmia, re-interventions, length of Intensive Care Unit (ICU) stay, length of hospital stay, readmissions), short-term mortality (30-day and 90-day), 3-year conditional survival (survival calculated after exclusion of combined 30-day/in-hospital mortality) and pathology results (R0-resection rate, circumferential resection margin (CRM), (positive) lymph node count). Accurate information on location of resected lymph nodes in the DUCA database is lacking. Since 2016, a division into five regions ('intrathoracic high' (paratracheal, laryngeal nerve, aorto-pulmonal), 'intrathoracic low' (subcarinal, paraesophageal), 'N1 gastric lymph node stations' (at least 3 out of 6), 'N2 gastric lymph node stations' (at least 3 out of 6) and distant lymph node stations) has been added to the registry. As the inclusion period of this study was January 2011 and December 2016, we cannot analyze location of resected lymph nodes in this complete cohort.

STATISTICAL ANALYSIS

Statistical analysis was performed with SPSS 26.0 software (SPSS, Inc., Chicago, IL, USA). The distribution of continuous variables was assessed using Shapiro-Wilk's test. For normally distributed continuous variables mean values with standard deviation (SD) were reported. In the case of not normally distributed continuous variables, median values with interquartile ranges (IQR) were reported. Binary and

categorical variables were reported as proportions. For the analysis of baseline patient and tumor characteristics, Mann-Whitney U test, student's t test, X²-test or Fisher's exact test were used where applicable. TTE and THE were analyzed separately because results may differ regarding morbidity and lymph node yield.

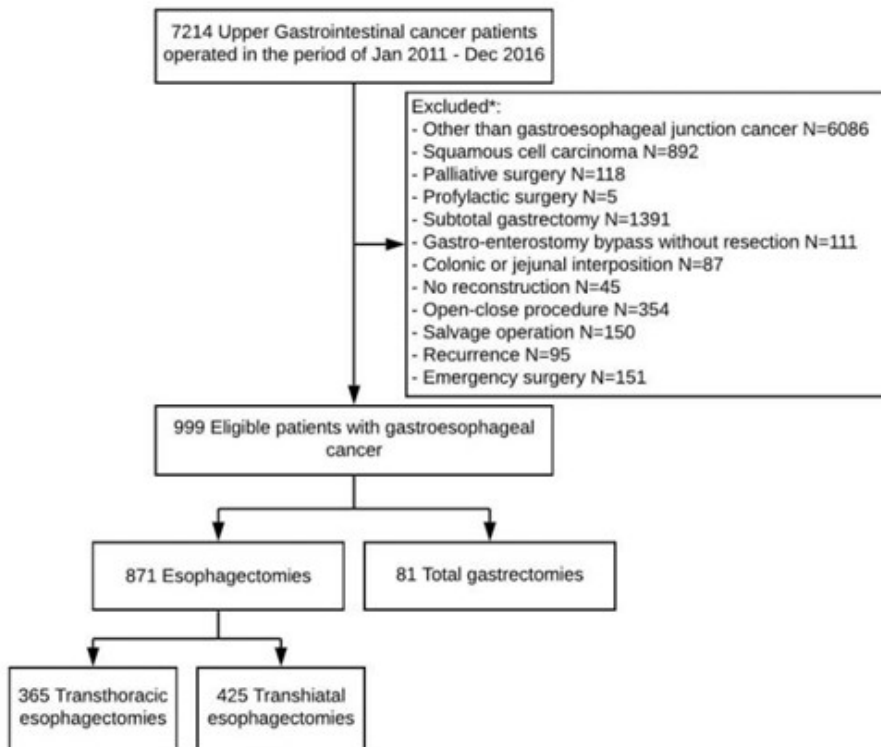
The 3-year overall and conditional survival was displayed using Kaplan Meier survival curves and analyzed using Cox regression analysis. Baseline patient and tumor characteristics with a p value <0.1 were added to the multivariable regression analysis as possible confounders using backwards stepwise method. The 3-year overall and conditional survival of patients after TTE, THE and total gastrectomy was compared to exclude the effect of heterogeneity in the esophagectomy group.

Subgroup analyses was performed in patients following perioperative chemotherapy, in patients following neoadjuvant chemoradiotherapy and in (y)pN+ patients. For the analysis of secondary outcomes (postoperative mortality, morbidity and pathology results) Mann-Whitney U test, student's t test, X²-test or Fisher's exact test were used where applicable and a Bonferroni correction for multiple testing was performed. If a p < 0.1 was found, postoperative morbidity, mortality and/or pathology results were entered in the multivariable analysis. Multivariable logistic regression was planned for dichotomous variables (postoperative morbidity, re-interventions, mortality, readmissions and R0 resection rate) and multivariable linear regression was planned for linear variables (length of ICU stay, length of hospital stay, CRM and (positive) lymph node count). A two-sided alpha of 0.05 was considered statistically significant.

RESULTS

DEMOGRAPHICS AND COHORT FEATURES

A total of 871 patients with GEJ cancer, out of 7214 registered upper gastrointestinal (Upper GI) cancer patients, were included in the analysis. 790 patients underwent an esophagectomy (365 TTE and 425 THE) and 81 patients underwent a total gastrectomy (Table 1). The reasons for patient exclusion can be found in the flowchart in figure 1. Most patients were male: 84.4% in the esophagectomy and 82.7% in the gastrectomy group. Patients following an esophagectomy were significantly younger than patients following a gastrectomy (median 65 years [IQR 58-70] vs median 68 years [IQR 60-74], $p=0.004$). Patients in the esophagectomy group received significantly more neoadjuvant treatment than patients in the gastrectomy group (92.5% vs 85.1%, $p<0.001$). The majority of patients receiving neoadjuvant treatment in the gastrectomy group received perioperative chemotherapy (83.8%) and the majority of patients in the esophagectomy group received neoadjuvant chemoradiotherapy (80.1%, $p<0.001$). An open approach was significantly less



*Excluded items are not mutually exclusive.

Figure 1: Study Flow Chart

TABLE 1: BASELINE PATIENT AND TUMOR CHARACTERISTICS OF PATIENTS AFTER TRANSTHORACIC OR TRANSHIATAL ESOPHAGECTOMY AND TOTAL GASTRECTOMY (N=871) IN THE PERIOD OF 2011-2016

	TRANSTHORACIC ESOPHAGECTOMIES		TRANSHIATAL ESOPHAGECTOMIES		ALL ESOPHAGECTOMIES		GASTRECTOMIES		P VALUE*
	N=365		N=425		N=790		N=81		
Gender (men)	312	(85.5)	355	(83.5)	667	(84.4)	67	(82.7)	0.687
Age (median [IQR], y)	64	[57-69]	66	[59-72]	65	[58-70]	68	[60-74]	0.004
BMI (median [IQR], kg/m²)	25.0	[23.0-28.0]	25.7	[23.3-29.0]	25.5	[23.1-28.4]	25.2	[22.7-27.7]	0.238
Comorbidity									
No	124	(34.0)	83	(19.5)	207	(26.2)	19	(23.5)	0.591
Yes	241	(66.0)	342	(80.5)	583	(73.8)	62	(76.5)	
Cardiac	73	(20.0)	116	(27.3)	189	(23.9)	28	(34.6)	0.035
Vascular	116	(31.8)	194	(45.6)	310	(39.2)	37	(45.7)	0.260
Diabetic	48	(13.2)	71	(16.7)	119	(15.1)	19	(23.5)	0.049
Pulmonary	47	(12.9)	76	(17.9)	123	(15.6)	18	(22.2)	0.122
Thrombotic	13	(3.6)	21	(4.9)	34	(4.3)	12	(14.8)	0.001
ASA									
1	82	(22.5)	61	(14.5)	143	(18.2)	10	(12.5)	0.012
2	216	(59.2)	249	(59.0)	465	(59.1)	39	(48.8)	
3	67	(18.4)	109	(25.8)	176	(22.4)	30	(37.5)	
4	0	0	3	(0.7)	3	(0.4)	1	(1.3)	
Neoadjuvant therapy									
No	20	(5.5)	39	(9.2)	59	(7.5)	12	(15.0)	<0.001
Yes	344	(94.5)	385	(90.8)	729	(92.5)	68	(85.1)	
Chemotherapy	57	(15.6)	88	(20.7)	145	(19.9)	57	(83.8)	<0.001
Chemoradiotherapy	287	(78.6)	297	(69.9)	584	(80.1)	11	(16.2)	
cT									
T0	0	0	0	0	0	0	0	0	0.581
T1	13	(3.7)	18	(4.4)	31	(4.1)	3	(4.0)	
T2	50	(14.4)	67	(16.5)	117	(15.5)	16	(21.3)	
T3	275	(79.0)	310	(76.2)	585	(77.5)	55	(73.3)	
T4	10	(2.9)	12	(2.9)	22	(2.9)	1	(1.3)	

cN	N0	125	(35.8)	154	(38.2)	279	(37.1)	28	(36.8)	0.634
	N1	137	(39.3)	168	(41.7)	305	(40.6)	28	(36.8)	
	N2	77	(22.1)	70	(17.4)	147	(19.5)	16	(21.1)	
	N3	10	(2.9)	11	(2.7)	21	(2.8)	4	(5.3)	
cM	M0	351	(99.2)	410	(99.5)	761	(99.3)	80	(98.8)	0.454
	M1	3	(0.8)	2	(0.5)	5	(0.7)	1	(1.2)	
Approach	Open	76	(20.8)	305	(71.8)	381	(48.2)	49	(60.5)	<0.001
	Hybrid	16	(4.4)	115	(27.0)	131	(16.6)	29	(35.8)	
	Minimal invasive	273	(74.8)	5	(1.2)	278	(35.2)	3	(3.7)	
Adjuvant therapy	No	329	(90.6)	363	(86.6)	692	(88.5)	39	(49.4)	<0.001
	Yes	34	(9.3)	56	(13.2)	90	(11.5)	40	(50.6)	
Chemotherapy		28	(82.4)	51	(91.1)	79	(87.8)	34	(85.0)	0.409
		6	(17.6)	5	(8.9)	11	(12.2)	5	(12.5)	
Radiotherapy		0	0	0	0	0	0	1	(2.5)	
		365	(100)	425	(100)	790	(100)	81	(100)	na
Histology	Adenocarcinoma	365	(100)	425	(100)	790	(100)	81	(100)	na
	T0	43	(12.3)	47	(12.1)	90	(12.2)	4	(12.5)	<0.001
	T1	47	(13.4)	59	(15.1)	106	(14.3)	3	(9.4)	
	T2	71	(20.3)	82	(21.0)	153	(20.7)	7	(21.9)	
	T3	185	(52.9)	200	(51.3)	385	(52.0)	13	(40.6)	
T4	4	(1.1)	2	(0.5)	6	(0.8)	5	(15.6)		
(y)pN	N0	182	(51.6)	203	(51.9)	385	(51.7)	15	(46.9)	0.305
	N1	80	(22.7)	84	(21.5)	164	(22.0)	6	(18.8)	
	N2	55	(15.6)	62	(15.9)	117	(15.7)	4	(12.5)	
	N3	36	(10.2)	41	(10.5)	77	(10.3)	7	(21.9)	
(y)pM	M0	348	(98.9)	405	(98.3)	753	(98.6)	76	(93.8)	0.013
	M1	4	(1.1)	7	(1.7)	11	(1.4)	5	(6.2)	

Data are presented as n (%) unless otherwise indicated. ASA = American Society of Anesthesiologists Classification. cTNM = clinical TNM staging classification before the treatment (AJCC 8th edition). IQR = interquartile range.*All esophagectomies vs gastrectomies. Bold p values represent significance. na = not applicable.

common in the esophagectomy group compared to the gastrectomy group (48.2% vs 60.5%, $p < 0.001$).

PRIMARY ENDPOINT: THE 3-YEAR OVERALL SURVIVAL

The Cox proportional hazards assumption was not violated, and Cox regression revealed that the 3-year overall survival was not significantly different between patients undergoing an esophagectomy or a gastrectomy (35.8% vs 28.4%, $p = 0.557$) after correction for the possible confounders age, operation date, comorbidities (cardiac, diabetic, thrombotic), ASA classification, neoadjuvant therapy (yes/no and chemoradiotherapy or chemotherapy), surgical approach (open, hybrid or minimally invasive), adjuvant therapy (yes/no), (y)pT stage and (y)pM stage (Table 4 and Figure 2A). The 3-year overall survival did not differ between a TTE, a THE and a total gastrectomy (supplementary figure 1A). Subgroup analyses in patients following perioperative chemotherapy, in patients following chemoradiotherapy and in (y)pN+ patients did not show differences in 3-year overall and conditional survival (supplementary figure 2-4). The number of gastrectomy patients in those subgroup analyses however, became so small, that strong conclusions cannot be drawn.

SECONDARY ENDPOINTS: 3-YEAR CONDITIONAL SURVIVAL, POSTOPERATIVE MORBIDITY, MORTALITY AND PATHOLOGY RESULTS

After univariable analysis and correction for multiple testing no significant difference was found in postoperative morbidity, 30-day and 90-day mortality, length of hospital stay, readmissions, re-interventions, positive lymph node count, R0 resection rate or median CRM between the esophagectomy and gastrectomy groups (Table 2). However, after univariable analysis a difference with a $p < 0.1$ between esophagectomy and gastrectomy groups was found in length of ICU stay (median 2 days [IQR 1-4] vs median 1 day [IQR 0-2], $p < 0.001$) and total lymph node count (median 17 [IQR 12-23] vs median 21 [IQR 16-31], $p < 0.001$). A multivariable linear regression was performed including a correction for the possible confounders age, operation date, comorbidities (cardiac, diabetic, thrombotic), ASA classification, neoadjuvant therapy (yes/no and chemoradiotherapy or chemotherapy), surgical approach (open, hybrid or minimally invasive), adjuvant therapy (yes/no), (y)pT stage and/or (y)pM stage. However, no significant difference was found between esophagectomy and gastrectomy in length of ICU stay ($\beta = 3.6$, 95% CI -0.043 – 7.292, $p = 0.053$) or total lymph node count ($\beta = -3.1$, 95% CI -6.446 – 0.165, $p = 0.063$) (Table 3). In addition, no significant difference was found in 3-year conditional survival between patients following an esophagectomy or a gastrectomy (36.9% vs 30.3%, $p = 0.470$) (Table 5 and Figure 2B). The 3-year conditional survival was also not significantly different between a TTE, a THE and a total gastrectomy (supplementary figure 1 B).

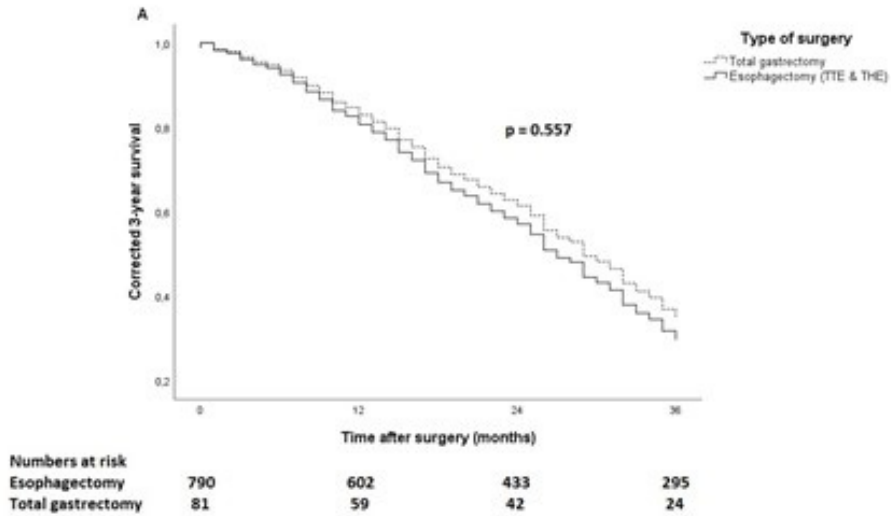


Figure 2 A: Corrected 3-year overall survival of patients with gastroesophageal junction cancer after an esophagectomy or a total gastrectomy.

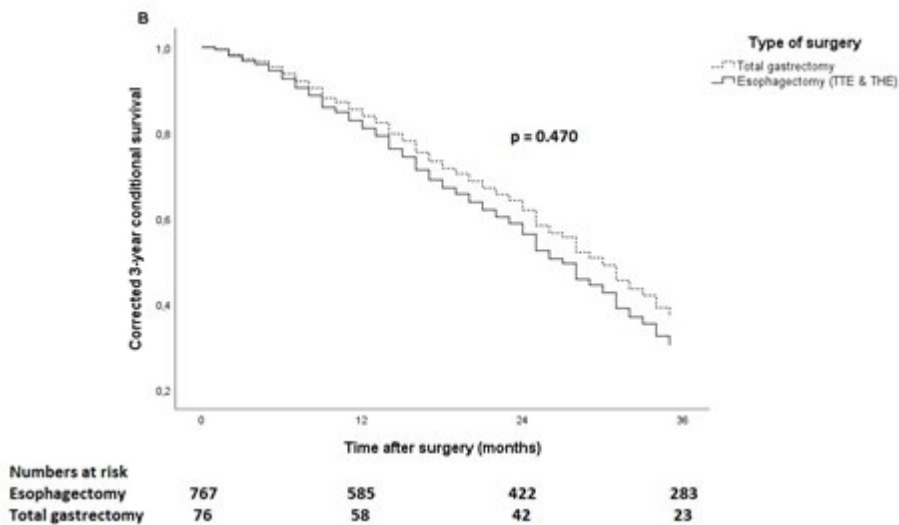


Figure 2 B: Corrected 3-year conditional survival of patients with gastroesophageal junction cancer after an esophagectomy.

TABLE 2: SECONDARY ENDPOINTS (POSTOPERATIVE MORBIDITY, MORTALITY AND PATHOLOGY RESULTS) OF 871 PATIENTS WITH GASTROESOPHAGEAL CANCER AFTER ESOPHAGECTOMY OR TOTAL GASTRECTOMY.

	TRANSTHORACIC ESOPHAGECTOMIES		TRANSHIATAL ESOPHAGECTOMIES		ALL ESOPHAGECTOMIES		GASTRECTOMIES		P VALUE*	CORRECTED P VALUE
	N=365	N=425	N=790	N=81						
Postoperative morbidity										
No	157 (43.0)	194 (46.2)	351 (44.7)	41 (50.6)	0.309	6.180				
Yes	208 (57.0)	226 (53.8)	434 (55.3)	40 (49.4)						
Anastomotic leakage	58 (17.6)	83 (20.1)	14 (18.2)	14 (18.2)	0.861	17.220				
Pulmonary complications	104 (28.5)	104 (24.8)	208 (26.5)	23 (28.4)	0.718	14.360				
Chyle leakage	37 (10.3)	4 (1.0)	41 (5.3)	3 (3.8)	0.790	15.800				
Cardiac complications	37 (10.1)	48 (11.5)	85 (10.8)	23 (28.4)	0.541	10.820				
Supraventricular arrhythmia	7 (4.2)	4 (2.0)	11 (3.0)	1 (2.3)	0.801	16.020				
Other	37 (10.1)	36 (8.6)	73 (9.3)	7 (8.6)	0.843	16.860				
Re-interventions										
Yes	94 (25.8)	71 (16.9)	165 (21.0)	25 (31.3)	0.036	0.720				
Radiologic	37 (39.8)	31 (45.6)	68 (42.2)	14 (56.0)	0.197	3.940				
Endoscopic	38 (40.9)	11 (16.4)	49 (30.6)	8 (32.0)	0.890	17.800				
Re-operation	55 (58.5)	48 (69.6)	103 (63.2)	14 (56.0)	0.490	9.800				
Length of ICU stay (median [IQR]. days)	2 [1-4]	1 [1-3]	2 [1-4]	1 [0-2]	<0.001	<0.001				

Length of hospital stay (median [IQR], days)	12	[9-19]	11	[9-16]	12	[9-17]	10	[8-19]	0.094	1.880
Readmissions	58	(16.1)	48	(11.4)	106	(13.4)	12	(14.8)	0.687	13.740
30-day/in-hospital mortality	6	(1.6)	13	(3.1)	19	(2.4)	3	(3.7)	0.450	9.000
90-day mortality	6	(1.6)	10	(2.4)	16	(2.0)	2	(2.5)	0.680	13.600
Resection rate	335	(92.3)	337	(90.0)	712	(91.0)	71	(87.7)	0.316	6.320
R1	28	(7.7)	39	(9.3)	67	(8.6)	10	(12.3)		
R2	0	0	3	(0.7)	3	(0.4)	0	0		
Circumferential resection margin (median [IQR], mm)	4	[2-8]	3	[1-6.5]	3	[1-7]	3.5	[1-10]	0.956	19.120
Total lymph node count (median [IQR])	20	[15-27]	15	[10-20]	17	[12-23]	21	[16-31]	<0.001	<0.001
Positive lymph node count (median [IQR])	0	[0-3]	0	[0-3]	0	[0-3]	1	[0-5]	0.138	2.760

Data are presented as N (%) unless otherwise indicated. IQR = interquartile range. *All esophagectomies vs gastrectomies. Bold p values represent significance.

TABLE 3: MULTIVARIABLE LINEAR REGRESSION ANALYSIS OF LYMPH NODE COUNT AND LENGTH OF INTENSIVE CARE UNIT STAY OF PATIENTS WITH GASTROESOPHAGEAL CANCER AFTER ESOPHAGECTOMY OR TOTAL GASTRECTOMY.

	COVARIATES	B	95% CI		P-VALUE
			LOWER	UPPER	
Lymph node count	<i>Esophagectomy</i>	-3.1	-6.446	0.165	0.063
	<i>Age</i>	-0.1	-0.198	-0.062	<0.001
	<i>Operation date</i>	0.7	0.283	1.108	0.001
	<i>Cardiac comorbidity</i>	-	-	-	-
	<i>Diabetes</i>	-	-	-	-
	<i>Thrombotic comorbidity</i>	-	-	-	-
	<i>ASA classification</i>	-	-	-	-
	<i>Neoadjuvant therapy</i>	-1.9	-3.018	-0.857	<0.001
	<i>Surgical approach</i>	2.1	1.555	2.563	<0.001
	<i>Adjuvant therapy</i>	2.2	0.055	4.273	0.044
	<i>(y)pT stage</i>	0.3	0.041	0.611	0.025
	<i>(y)pM stage</i>	-6.4	-11.150	-1.661	0.008
Length of ICU stay	<i>Esophagectomy</i>	3.6	-0.043	7.292	0.053
	<i>Age</i>	-	-	-	-
	<i>Operation date</i>	-	-	-	-
	<i>Cardiac comorbidity</i>	-	-	-	-
	<i>Diabetes</i>	-	-	-	-
	<i>Thrombotic comorbidity</i>	-	-	-	-
	<i>ASA classification</i>	2.0	0.861	3.132	0.001
	<i>Neoadjuvant therapy</i>	-0.7	-1.982	0.494	0.239
	<i>Surgical approach</i>	0.3	-0.186	0.873	0.204
	<i>Adjuvant therapy</i>	-1.2	-3.579	1.248	0.343
	<i>(y)pT stage</i>	-0.2	-0.481	0.166	0.338
	<i>(y)pM stage</i>	-	-	-	-

B = regression coefficient, CI = confidence interval. ICU = Intensive Care Unit. ASA = American Society of Anesthesiologists Classification. *All esophagectomies vs gastrectomies. Bold p values represent significance.

TABLE 4: COX REGRESSION OF THE 3-YEAR OVERALL SURVIVAL OF PATIENTS WITH GASTROESOPHAGEAL CANCER AFTER AN ESOPHAGECTOMY OR A TOTAL GASTRECTOMY.

	HAZARD RATIO	95% CI		P VALUE
		LOWER	UPPER	
Esophagectomy	1.2	0.721	1.836	0.557
Age	1.0	0.986	1.007	0.491
Operation date				<0.001
2011	1.1	0.735	1.636	0.652
2012	1.4	0.965	2.157	0.074
2013	2.0	1.410	2.929	<0.001
2014	5.0	3.456	7.372	<0.001
2015	10.0	6.703	15.029	<0.001
Cardiac comorbidity	1.0	0.768	1.220	0.782
Diabetes	1.2	0.915	1.520	0.203
Thrombotic comorbidity	1.2	0.786	1.820	0.404
ASA classification				0.372
ASA 1	1.1	0.878	1.454	0.343
ASA 2	1.3	0.962	1.831	0.085
ASA 3	1.1	0.362	3.167	0.902
Neoadjuvant therapy	1.1	0.912	1.285	0.365
Surgical approach	1.0	0.955	1.106	0.468
Adjuvant therapy	0.9	0.655	1.251	0.546
(y)pT stage	1.1	1.068	1.169	<0.001
(y)pM stage	1.1	0.602	2.121	0.704

ASA classification = American Society of Anesthesiologists classification. Bold p values represent significance.

TABLE 5: COX REGRESSION OF THE 3-YEAR CONDITIONAL SURVIVAL OF PATIENTS WITH GASTROESOPHAGEAL CANCER AFTER AN ESOPHAGECTOMY OR A TOTAL GASTRECTOMY.

	HAZARD RATIO	95% CI		P VALUE
		LOWER	UPPER	
Esophagectomy	1.2	0.735	1.951	0.470
Age	1.0	0.985	1.006	0.366
Operation date				<0.001
2011	1.1	0.697	1.590	0.806
2012	1.4	0.914	2.092	0.125
2013	2.1	1.439	3.031	<0.001
2014	5.1	3.454	7.514	<0.001
2015	10.9	7.189	16.468	<0.001
Cardiac comorbidity	0.9	0.726	1.174	0.517
Diabetes	1.1	0.881	1.494	0.309
Thrombotic comorbidity	1.2	0.793	1.870	0.369
ASA classification				0.569
ASA 1	1.1	0.868	1.442	0.387
ASA 2	1.3	0.913	1.761	0.157
ASA 3	1.2	0.392	3.480	0.780
Neoadjuvant therapy	1.1	0.911	1.300	0.350
Surgical approach	1.0	0.966	1.122	0.290
Adjuvant therapy	1.0	0.694	1.332	0.813
(y)pT stage	1.1	1.072	1.177	<0.001
(y)pM stage	1.1	0.554	2.072	0.837

ASA classification = American Society of Anesthesiologists classification. Bold p values represent significance.

DISCUSSION

This study investigated the long-term survival, postoperative morbidity, mortality and pathology results in patients following an esophagectomy or a total gastrectomy for GEJ cancer. The results show that the 3-year overall and conditional survival of patients with GEJ cancer undergoing either an esophagectomy or a gastrectomy did not differ significantly. In addition, postoperative morbidity, short-term mortality and pathology results were not different between the two surgical approaches. Although not in line with our hypothesis, the study results contribute to clinical decision making by showing that both procedures can be performed with comparable short- and long-term results for patients with GEJ cancer. In addition, a recent study showed that the majority of patients have significant symptoms more than one year following an esophagectomy²⁰, however, largely comparable results were found between a gastrectomy and an esophagectomy regarding long-term quality of life²¹. Therefore, surgeons can base their decision with respect to the operative procedure for patients with GEJ cancer on personal and center experience.

A high heterogeneity was observed across previous studies investigating long-term survival, morbidity, mortality and pathology results in patients following an esophagectomy or a total gastrectomy^{8,9}. In some studies, administration of neoadjuvant therapy was either excluded or not reported and most studies also included distal esophageal or cardia/gastric cancers, rendering the comparison with our results difficult. Nonetheless, two systematic reviews, mostly comprised of retrospective mono-center studies, reported no significant difference in 5-year overall survival, 30-day mortality, lymph node yield or radicality of surgery, although a higher rate of postoperative morbidity was seen after esophagectomy in one. The most recent systematic review included one randomized controlled trial (RCT)²². This RCT compared patients after left thoracoabdominal approach (N=85) versus abdominal- transhiatal approach (N=82) and found no significant difference in 5-year overall survival but increased morbidity after left thoracoabdominal approach. In this RCT only patients with (sub)cardia cancer were included and all patients were operated by an open approach via a left thoracoabdominal incision, and therefore, the results of this RCT cannot be directly compared to the present study. Furthermore, a recent study with the national audit data (DUCA) compared the quality of the surgical resection, morbidity and mortality between a TTE and a THE esophagectomy in patients with a distal esophageal or GEJ cancer [23]. In this study, an increased morbidity and short-term mortality was found in the transthoracic group, but also a higher lymph node yield. However, long-term survival was not investigated. In the present study, a subgroup analysis of 3-year overall and conditional survival between TTE and THE was performed and showed no significant difference between the two groups. However, these results are only applicable to patients with GEJ cancer.

In the Netherlands, centralization of esophageal cancer surgery was initiated in 2011, whereas centralization of gastric cancer surgery was initiated two years later, in 2013. Since then, a minimum of 20 esophagectomies and 20 gastrectomies yearly is required to perform either gastrectomies or esophagectomies at a center. Mortality rates for gastrectomy have dropped from 7.7% in 2011 to 4.4% in 2018, while mortality rates following esophagectomy have dropped as well, but were already much lower compared to gastrectomy (4.1% in 2011 and 2.7% in 2018)^{2,24}. This delayed centralization for gastrectomies may partially explain why a higher morbidity following gastrectomy was observed in this population-based study. In addition, the pathology results, with a high R0 resection and similar (y)pN0 rate in both groups probably contribute to the comparable survival rates in both groups, even though a higher (y)pT4 rate was observed in the gastrectomy group.

Furthermore, minimally invasive esophagectomy is associated with less pulmonary complications compared to open esophagectomy²⁵. Minimally invasive esophagectomy has become the preferred approach in the Netherlands, where 90.9% of all esophagectomies were performed minimally invasively in 2018². Also, in this study the majority of patients were operated minimally invasively, perhaps that is why less postoperative morbidity than expected was observed in the esophagectomy group. The comparable postoperative morbidity results may also contribute to similar long-term survival, as has been shown that survival may impair in patients with severe complications¹².

Various retrospective studies have been unable to determine the optimal extent of lymph node dissection for GEJ cancer²⁶⁻²⁸. A recent prospective study investigated the incidence of lymph node metastases in each lymph node station in patients with a GEJ tumor. They found a >10% rate of lymph node metastases in stations 1, 2, 3, 7, 9, and 11p, and at least 1 of the lower mediastinal lymph node stations. If esophageal involvement exceeded 4 cm, station 106recR (right recurrent laryngeal nerve) was also affected in more than 10% of the cases and other upper middle and lower mediastinal lymph node stations were regularly affected. Therefore, the authors propose to perform a right transthoracic approach in all patients with a GEJ tumor that invades the esophagus for more than 4 cm²⁹. Unfortunately, such detailed information in the DUCA database is lacking. The registration of the location of resected lymph nodes in the DUCA database started in 2016 and the location of lymph node metastases is not recorded. Therefore, we could only provide information about whether a lymphadenectomy was performed. Due to a thoracic as well as an abdominal phase of the surgery we expected more lymph nodes to be resected in patients who underwent an esophagectomy. We found no significant difference in total lymph node count however, between patients who underwent an esophagectomy or a gastrectomy. Also, there was no significant difference in

positive lymph node count or radicality of surgery. Our findings are in accordance with a recent systematic review where also no difference in total lymph node count and R0-resection rate was found between esophagectomy and gastrectomy in patients with GEJ cancer⁸.

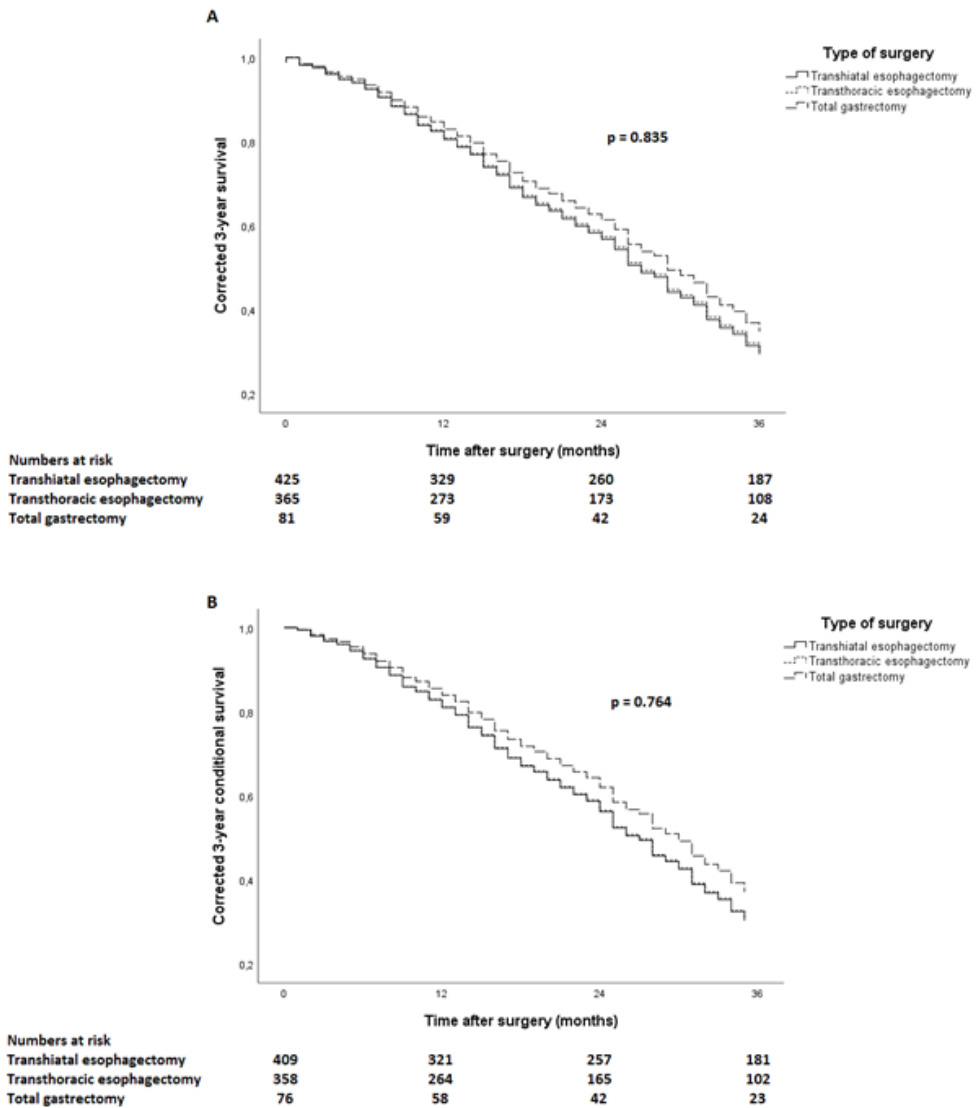
A large difference in the number of patients with GEJ cancer treated with either an esophagectomy or a gastrectomy is seen in our data. Apparently, in the Netherlands, a preference for an esophagectomy exists for patients with GEJ cancer, although the reasons for this selection are unknown. This preference could be based on tumor characteristics (e.g. slightly more ingrowth in the distal esophagus), on surgeon's experience or expert opinion, there are however no data to support this.

The present study has several limitations. It is a retrospective comparative cohort study of prospectively collected data and no propensity score matching could be performed as it would have highly reduced the number of included patients with GEJ cancer who underwent a total gastrectomy. Furthermore, the DUCA-VEKTIS database was merged on the 1st of September 2017, and therefore no survival data after this date were available. Also, no disease specific survival could be analyzed as the cause of death is neither reported in the DUCA nor VEKTIS database. Since DUCA only recently added the Clavien-Dindo classification for postoperative complications to the audit, these data were unavailable for the vast majority of our cohort, and as such could not be analyzed. The anatomical location of the GEJ cancer could not be classified according to the Siewert-Stein classification [30], as it is not included in the DUCA database. However, extensive input options for esophageal tumor location are available in the DUCA database, including cervical, proximal intrathoracic, mid- thoracic, distal thoracic and esophagus-stomach transition point and this choice is made by the responsible surgeon. The number of statistical tests performed was high, therefore, a Bonferroni correction for multiple testing was performed, to counteract the possibility of finding a significant difference by chance. Furthermore, this study does not include any patient-reported outcome measures.

A strength of the current multicenter study in the Netherlands is that it includes one of the largest samples of patients with GEJ cancer with long-term survival data at a population level.

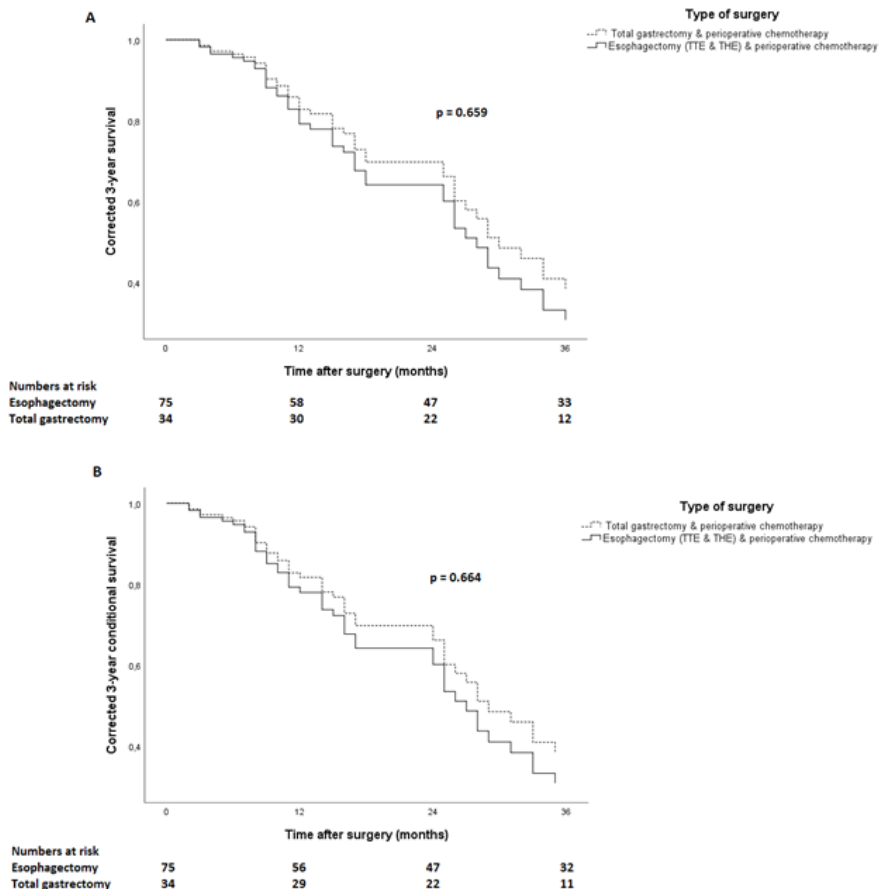
In conclusion, this study shows that an esophagectomy and a total gastrectomy in patients with GEJ cancer show largely comparable results with regard to postoperative morbidity and mortality, pathology results as well as long-term survival. Other parameters such as surgeon's experience should be considered when planning surgery if both procedures are technically feasible. However, these results need confirmation by randomized controlled trials.

Gastrectomy versus Esophagectomy For Gastroesophageal Junction Tumors



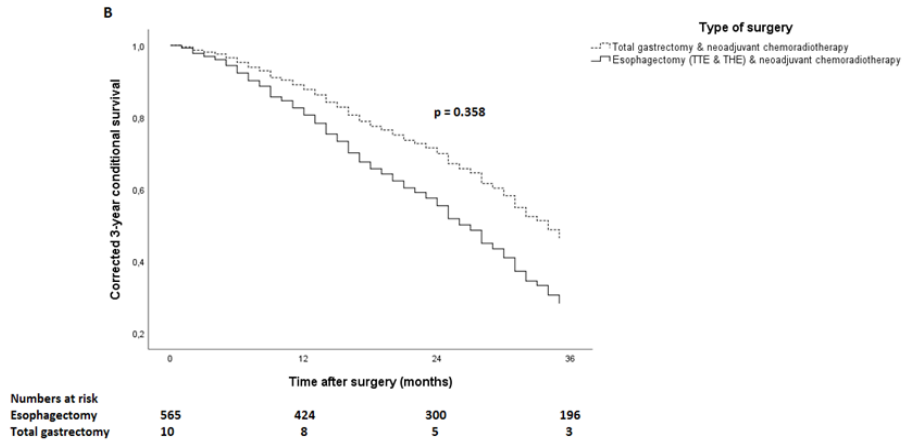
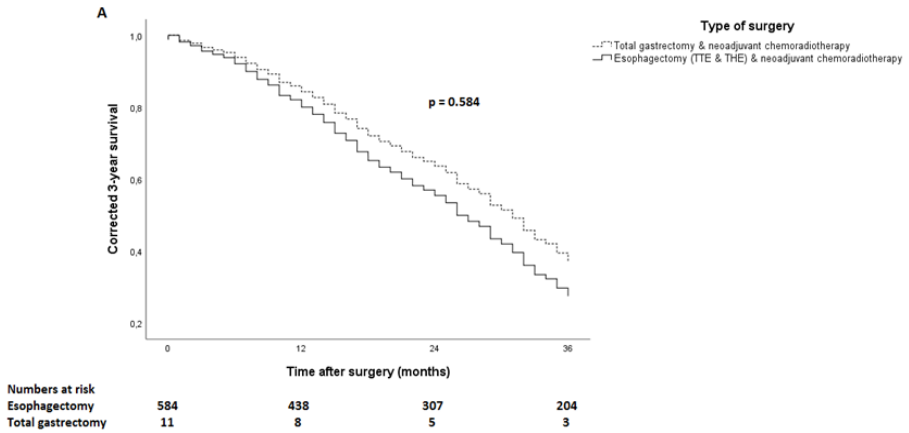
Supplementary figure 1 A & B: A: corrected 3-year overall survival of patients with gastroesophageal junction cancer after transhiatal esophagectomy, transthoracic esophagectomy or total gastrectomy. B: corrected 3-year conditional survival of patients with gastroesophageal junction cancer after transhiatal esophagectomy, transthoracic esophagectomy or total gastrectomy

Gastrectomy versus Esophagectomy For Gastroesophageal Junction Tumors



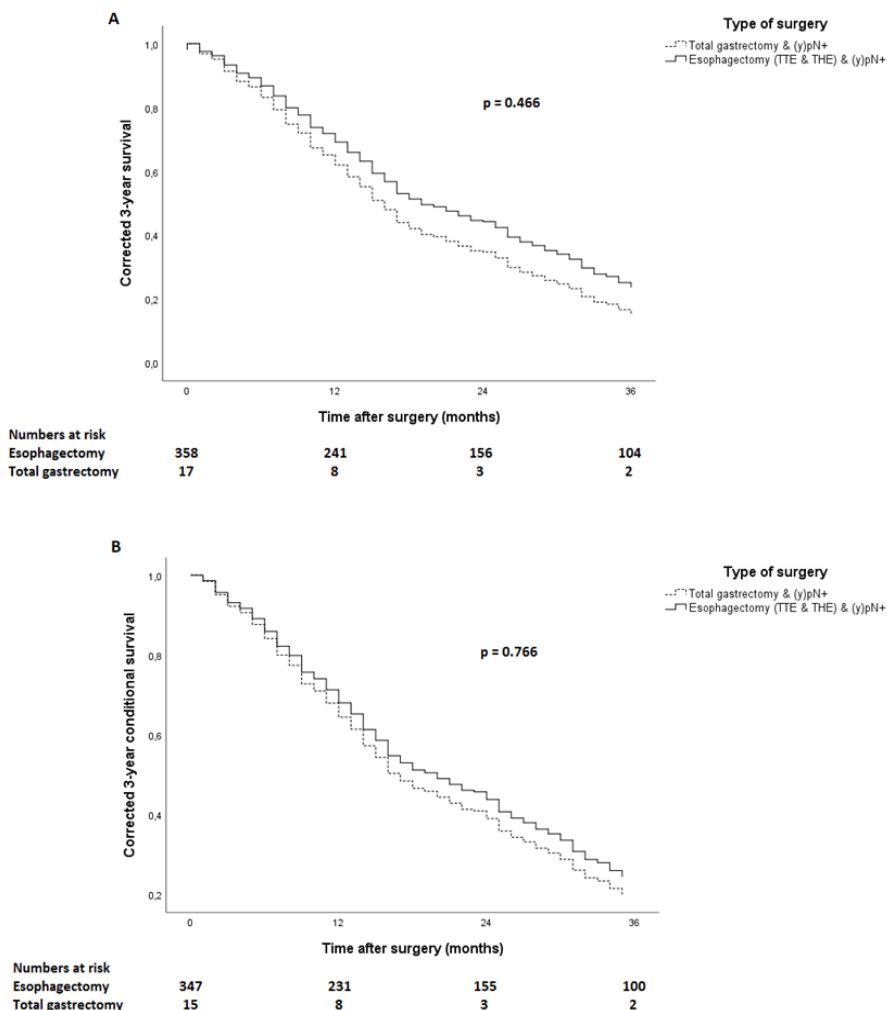
Supplementary figure 2 A & B: A: corrected 3-year overall survival of patients with gastroesophageal junction cancer after esophagectomy (THE=transhiatal, TTE=transthoracic) & perioperative chemotherapy or total gastrectomy & perioperative chemotherapy. B: corrected 3-year conditional survival of patients with gastroesophageal junction cancer after esophagectomy (THE=transhiatal, TTE=transthoracic) & perioperative chemotherapy or total gastrectomy & perioperative chemotherapy.

Gastrectomy versus Esophagectomy For Gastroesophageal junction Tumors



Supplementary figure 3 A & B: A: corrected 3-year overall survival of patients with gastroesophageal junction cancer after esophagectomy (THE=transhiatal, TTE=transthoracic) & neoadjuvant chemoradiotherapy or total gastrectomy & neoadjuvant chemoradiotherapy. B: corrected 3-year conditional survival of patients with gastroesophageal junction cancer after esophagectomy (THE=transhiatal, TTE=transthoracic) & neoadjuvant chemoradiotherapy or total gastrectomy & neoadjuvant chemoradiotherapy.

Gastrectomy versus Esophagectomy For Gastroesophageal Junction Tumors



Supplementary figure 4 A & B: A: corrected 3-year overall survival of patients with gastroesophageal junction cancer after esophagectomy (THE=transhiatal, TTE=transthoracic) & (y)pN+ (positive lymph node burden) or total gastrectomy & (y)pN+. B: corrected 3-year conditional survival of patients with gastroesophageal junction cancer after esophagectomy (THE=transhiatal, TTE=transthoracic) & (y)pN+ (positive lymph node burden) or total gastrectomy & (y)pN+.

REFERENCES

1. Bartel, M., B. Brahmbhatt, and A. Bhurwal, Incidence of gastroesophageal junction cancer continues to rise: Analysis of Surveillance, Epidemiology, and End Results (SEER) database. *Journal of Clinical Oncology*, 2019. 37(4_suppl): p. 40-40.
2. DICA. 2018; Available from: <https://dica.nl/jaarrapportage-2018/duca>.
3. Hulscher, J.B., et al., Transthoracic versus transhiatal resection for carcinoma of the esophagus: a meta-analysis. *Ann Thorac Surg*, 2001. 72(1): p. 306-13.
4. Straatman, J., et al., Minimally Invasive Versus Open Esophageal Resection: Three- year Follow-up of the Previously Reported Randomized Controlled Trial: the TIME Trial. *Ann Surg*, 2017. 266(2): p. 232-236.
5. Kodama, I., et al., Lymph node metastasis and lymphadenectomy for carcinoma in the gastric cardia: clinical experience. *Int Surg*, 1998. 83(3): p. 205-9.
6. Mariette, C., et al., Surgical management of and long-term survival after adenocarcinoma of the cardia. *Br J Surg*, 2002. 89(9): p. 1156-63.
7. Ito, H., et al., Adenocarcinoma of the gastric cardia: what is the optimal surgical approach? *J Am Coll Surg*, 2004. 199(6): p. 880-6.
8. Heger, P., et al., Thoracoabdominal versus transhiatal surgical approaches for adenocarcinoma of the esophagogastric junction-a systematic review and meta- analysis. *Langenbecks Arch Surg*, 2019. 404(1): p. 103-113.
9. Haverkamp, L., et al., Systematic review of the surgical strategies of adenocarcinomas of the gastroesophageal junction. *Surg Oncol*, 2014. 23(4): p. 222- 8.
10. DUCA. October 2019; Available from: <https://dica.nl/duca/home>.
11. Vektis. [cited 2019; Available from: <https://www.vektis.nl/over-vektis>.
12. van der Werf, L.R., et al., A National Cohort Study Evaluating the Association Between Short-term Outcomes and Long-term Survival After Esophageal and Gastric Cancer Surgery. *Ann Surg*, 2019. 270(5): p. 868-876.
13. von Elm, E., et al., The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*, 2008. 61(4): p. 344-9.
14. Oncoline. 2020; Available from: <https://www.oncoline.nl/maagcarcinoom>.
15. Oncoline. <https://www.oncoline.nl/oesofaguscarcinoom>. 2020.
16. Shapiro, J., et al., Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *Lancet Oncol*, 2015. 16(9): p. 1090-1098.
17. Ostwal, V., et al., Perioperative Epirubicin, Oxaliplatin, and Capecitabine Chemotherapy in Locally Advanced Gastric Cancer: Safety and Feasibility in an Interim Survival Analysis. *J Gastric Cancer*, 2017. 17(1): p. 21-32.
18. Cats, A., et al., Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. *Lancet Oncol*, 2018. 19(5): p. 616-628.
19. guidelines, N. https://www.nccn.org/professionals/physician_gls/default.aspx#site. 2020.

20. Markar, S.R., et al., Lasting Symptoms After Esophageal Resection (LASER): European Multicenter Cross-sectional Study. *Ann Surg*, 2020.
21. Jezerskyte, E., et al., Long-Term Quality of Life After Total Gastrectomy Versus Ivor Lewis Esophagectomy. *World J Surg*, 2020. 44(3): p. 838-848.
22. Sasako, M., et al., Left thoracoabdominal approach versus abdominal-transhiatal approach for gastric cancer of the cardia or subcardia: a randomised controlled trial. *The Lancet Oncology*, 2006. 7(8): p. 644-651.
23. Mertens, A.C., et al., Transthoracic Versus Transhiatal Esophagectomy for Esophageal Cancer: A Nationwide Propensity Score-Matched Cohort Analysis. *Annals of Surgical Oncology*, 2020.
24. DICA. <https://dica.nl/jaarrapportage-2016/duca>. 2016.
25. Biere, S.S.A.Y., et al., Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. *The Lancet*, 2012. 379(9829): p. 1887-1892.
26. Yoshikawa, T., et al., Theoretical therapeutic impact of lymph node dissection on adenocarcinoma and squamous cell carcinoma of the esophagogastric junction. *Gastric Cancer*, 2016. 19(1): p. 143-9.
27. Kurokawa, Y., et al., Mediastinal lymph node metastasis and recurrence in adenocarcinoma of the esophagogastric junction. *Surgery*, 2015. 157(3): p. 551-5.
28. Yamashita, H., et al., Optimal extent of lymph node dissection for Siewert type II esophagogastric junction carcinoma. *Ann Surg*, 2011. 254(2): p. 274-80.
29. Kurokawa, Y., et al., Mapping of Lymph Node Metastasis From Esophagogastric Junction Tumors: A Prospective Nationwide Multicenter Study. *Ann Surg*, 2019.
30. Siewert, J.R. and H.J. Stein, Classification of adenocarcinoma of the oesophagogastric junction. *Br J Surg*, 1998. 85(11): p. 1457-9

CHAPTER TWELVE

General discussion and future perspectives



GENERAL DISCUSSION AND FUTURE PERSPECTIVES

This thesis is comprised of a number of studies on a broad spectrum of pathologies of the upper gastro-intestinal tract. Part I focusses on the optimal treatment of benign pathology: reflux, hiatal hernias and high-tech surgery in general. Part II contains studies on the perioperative risks of surgical treatment of malignancy in the upper gastrointestinal tract, specifically the esophagus and stomach.

PART I: REFLUX, HIATAL HERNIAS AND HIGH-TECH SURGERY

Gastro-intestinal reflux is a very common disease in adults. The treatment options can range from medication to endoscopic procedures or surgical interventions. This thesis focuses on surgical interventions. When interpreting the results from the studies in part I, it is important to consider that most patients will experience sufficient relief of symptoms through medication and only a small proportion will consider a surgical consult for acid reflux.

Those patients that do end up in the outpatient clinic of a surgeon specialized in reflux disease, have often tried every other more conservative treatment option available. These patients are often unable to lie flat in bed, have to avoid a broad spectrum of drinks and food in order to manage their symptoms, and often this at best only alleviates complaints. The disease can be very socially limiting, and in extreme cases patients experience regurgitation of food and dental erosion. This context is essential when trying to understand why someone would contemplate undergoing surgery for an essentially benign disease: even though reflux is considered a benign disease, acid exposure of the esophagus can lead to metaplasia and even esophageal cancer. These worst-case scenarios can be enough to seek out treatment of the underlying problem, but on the other hand it is prudent to avoid surgery when the risks do not outweigh the benefits.

This thesis focusses on the fraction of patients that have acid reflux due to (or at least in the presence of) a hiatal hernia. Although funduplications are effective in the absence of a hiatal hernia, the presence of one adds a significant complexity to the procedure. Modern antireflux surgery consists of repairing any hernia of the diaphragm if present, followed by folding and suturing the gastric fundus around the esophagus in order to support the lower esophageal sphincter in its function. Both the closure of a hiatal hernia and the construction of a fundoplication are performed based on experience of the surgeon. As of the time of writing this thesis, there is no objective method that allows the surgeon to determine the optimal tension on a hernia repair, the optimal opening of the repair, or the tightness of the fundoplication. If a hernia repair or the fundoplication is too tight, the patient will suffer dysphagia. If it is too loose, the fundoplication can slip into the thoracic cavity

with a high likelihood of recurrent symptoms, and minimal to absent reflux control. For this reason, surgeons performing this procedure need extensive experience.

Although anti-reflux surgery is considered a routine procedure for an experienced surgeon, it can easily lead to intraoperative complications. As described in chapter 2, the procedure generally involves ligation of the short gastric vessels in order to mobilize the spleen, reduce and resect the hernia sac from the diaphragm close to the pleura, heart, aorta and vena cava. The esophagus and stomach can be damaged through tension, puncture by a suturing needle or instrument pressure, and failure to recognize this can lead to significant infections. Aside from complications, recovery is not without its caveats either. The altered anatomy will mean that passage of gastric acid to the esophagus is majorly decreased, but if the fundoplication is too tight the passage of food to the stomach will also be impaired. This can cause severe pain when attempting to start a normal diet postoperatively. For this reason, patients start out with a liquid diet postoperatively, and within a few weeks most patients are able to resume their regular diet.

In the past, reflux surgery has had a fairly negative reputation. This was partly due to a low percentage of relief of symptoms postoperatively, and partly due to the chance of a recurrence. Even with all the skill accrued by expert surgeons, up to 40% of patients will experience a recurrent hernia and around 10% will require redo surgery¹⁻⁴. The disconnect between the 40% recurrence and the amount of patients that require subsequent surgery is most likely caused by the fact that even a slipped fundoplication can in many cases provide adequate reflux control^{5,6}. As a result, redo surgery is only indicated in patients with serious symptoms that can be correlated to a recurrence of the hernia. Radiological or esophagogastrosopic evidence of a recurrence in the absence of symptoms or alarming characteristics should never be taken as an indication for surgical treatment.

The reason that one should be hesitant to perform redo surgery based on anatomical recurrence alone is that redo surgery is a lot more difficult to perform and carries greater risks to the patient. As described in chapter 3, the core of this reasoning is that redo surgery carries a greater risk of vagal nerve damage, bleeding and perforation due to scar tissue. It is difficult to undo a prior fundoplication as the sutures may be embedded in scar tissue, and the entire operating area can be difficult to access for the same reason. While bleeding and infection can generally be successfully managed, vagal nerve damage can be permanent. Nerve damage might lead to temporary slowed gastric emptying with the accompanying indigestion, nausea and even vomiting. If the nerve gets severed this will often be permanent or require another procedure.

All these considerations do not mean that surgical treatment should be kept from patients at all costs. When performed in a high-volume center, even redo surgery can be carried out with high success rates and low risks⁷⁻¹⁶. Chapter 5 describes the results from one of these centers. The relatively low risks, combined with the symptomatology that these patients experience, do not call for avoiding surgical treatment as long as the surgeon performing the procedure has sufficient expertise. In line with this, determining if surgical treatment is prudent for a patient should only be done by an expert in the field. Interpreting the available diagnostic tools such as CT-scanning, barium-esophagograms, pH-/manometry and gastric emptying studies requires specialized training. In chapter 7, we studied the accuracy of assessing the anatomy of the gastro-esophageal junction and hiatal hernias on CT imaging when performed by experts. As described in this chapter it is not sufficient to look at the results of imaging alone when diagnosing failed antireflux surgery. Instead, the composite of functional testing, imaging and a detailed patient history are required for an accurate diagnosis.

A recurring theme in the studies of part I of this thesis is the use of robotic assistance during surgery. Robotic assistance enables the surgeon to perform incredibly precise actions from a sitting position, a close-up 3D view while technically performing laparoscopic procedure. In chapter 3 we describe the intricacies of redo surgery when using a robotic system up to a third redo. Without robotic assistance, many of the patients described in chapter 5 would not have been treated due to the increased risks of the alternative approach: open surgery. As stated before, redo surgery can be difficult due to adhesions and scar tissue. When performing laparoscopic surgery, the surgeon does not feel the tissue as he/she would during an open procedure. While there is some haptic feedback, hand movements do not align 1:1 with the instrument tip, and it is very easy to pull too hard or miss the target altogether. Although robotic surgery further eliminates haptic feedback – it is completely absent -, the increased visibility and precise movements allow very delicate dissection of adhesions¹⁷⁻¹⁹. A robotic assisted laparoscopic surgery provides the same shortened hospital stay as a normal laparoscopic procedure. This is opposed to a longer stay for open surgery along with the increased risks of infection, long-term risks such as incisional herniation and the longer recovery time associated with a laparotomy. In other words, robotic assisted surgery extends the possibilities of laparoscopic surgery by overcoming part of the technical limitations native to conventional laparoscopic surgery¹⁷⁻¹⁹.

As robotic assisted surgery was only introduced at the start of this century, the learning curve has been steep. Where early studies focused on proving that this type of procedure would at least provide equivalent outcomes to conventional laparoscopic surgery, the focus has started to shift towards proving that it is superior

and does not increase the costs of surgery. The costs of robotic systems have been a major point of discussion amongst surgeons and hospital boards since the introduction of the first FDA-approved system in 2000. These systems use a lot of patented disposable materials and require expensive maintenance. At the same time studies often show an increased operative time, and even in surgery the age-old adage holds true: time is money. One minute of time spent in the operation theatre costs upwards of a few hundred dollars, so it stands to reason that any additional time spent in surgery should be avoided. Robotic systems often take more time to set up correctly than a laparoscopic or open procedure, and the surgery itself can also take longer.

While there are many possible explanations for this, lack of experience and a more complex caseload seem logical factors. Almost all modern surgeons are trained in laparoscopic surgery, but robotic systems are generally not part of the curriculum. The study described in chapter 6 shows that operating times in an experienced robotic center are not significantly longer than laparoscopic surgery. This chapter also explores another two complicating factors in research into operating times: registration and reporting bias. Literature review showed that studies seldomly accurately report on operating times and reported times are often ill-defined, which makes comparison meaningless. No researcher would compare outcomes that were measured on different scales, but operating times are often compared directly, even though the report does not state whether the reported time concerns to the total time spent in the operating theatre, skin to skin time, or any variation on these measures.

As operating time decreases and morbidity and mortality have been minimized as far as current technology allows, it is perhaps time to put the spotlight on factors regarding quality of life. One of these factors is postoperative pain. Antireflux surgery is now very safe, and can be performed in an acceptable amount of time. One of the steps historically associated with creating a fundoplication is the ligation of gastrosplenic ligament containing the short gastric vessels. Ligating this ligament (and consequently the short gastric vessels contained within it), allows mobilization of the normally fixated gastric fundus. As the stomach is fairly mobile after this, the next step of wrapping the stomach around the esophagus is made a lot easier. Recent studies, however, put the necessity of this step up for discussion²⁰⁻²⁵. Reports show that a fundoplication can be performed in most, if not all, cases without ligating the gastrosplenic ligament. The rationale behind leaving the ligament intact is that the short gastric vessels are part of the blood supply to the spleen and gastric fundus, and therefore ligating these can lead to splenic infarction. Splenic infarctions are reported in around 1% of patients that undergo antireflux surgery, but these numbers are based on patients that report ongoing pain for the first several

weeks postoperatively. It could be the case that a lot more of these infarctions occur than the literature seems to suggest, and most resolve without intervention. Pain originating from a splenic infarct is located in the left upper quadrant of the abdomen, where many patients describe symptoms of postoperatively pain.

The fact that a high likelihood of spontaneous recovery is plausible does not distract at all from the need to minimize even temporary side-effects of antireflux surgery. Chapter 4 explores the feasibility of assessing the vascularization of the spleen during antireflux surgery by means of near-infrared fluoroscopy. In this study, we did find definite intraoperative vascularization defects in two of the ten patients that developed immediately after ligating the gastrosplenic ligament. Although the small sample size of ten patients is not enough to discredit the reported incidence of 1% in the scientific canon, it does merit further research. If there is indeed a correlation between ligating the gastrosplenic ligament and postoperative pain, it would be wise to attempt to leave the ligament intact whenever possible.

PART II: MALIGNANT DISEASE

The theme of determining the impact of surgical treatment on morbidity, and indirectly quality of life, continues in part II of this thesis. Gastric and esophageal cancer are both in the top 10 of cancer-related deaths worldwide²⁶⁻²⁸, and surgery is still the cornerstone of treatment. Surgical treatment has largely moved from open surgery to laparoscopic, and even robotic surgery is becoming more common. Simultaneously, large gains in survival have been attained with improved (neo) adjuvant treatment schemes. The exact procedure of choice is still a matter of active debate: which patients should not be operated on and in those who should, which variant of a surgical procedure to perform.

Chapter 8 discusses the merits of attempting curative gastrectomy in patients with gastric cancer that are over 70 years old. Older patients generally have more morbidity, and therefore a larger chance of complications during or after surgery. These comorbidities can also come into play when (neo)adjuvant therapy is considered. Publications from Dutch cancer audits show that for several types of malignancy, patients over the age of 70 are at an increased risk of complications and mortality, even when correcting for pre-existing conditions. The analysis on retrospective data on patients with gastric cancer in this chapter shows that this holds true for gastric cancer. The choice to proceed to surgery should always be made in consultation with the patient as a shared decision with this in mind.

When a patient suffers from curable gastric cancer in the middle part of the stomach, treatment can consist of partial or complete gastric resection. The optimal resection pattern becomes less obvious when the tumor is located at the gastro-esophageal junction: at the intersection of the esophagus and stomach. Chapter 11

is an attempt to determine if the surgical treatment should involve a gastrectomy or esophagectomy. There is evidence pointing to either of these options as the superior choice, meaning that treatment is often based on expert opinion rather than objective scientific proof. There are several large-scale efforts underway to prospectively determine the optimal course of action, but until the results of those studies have been published nobody has the answer. The study described in this chapter compares the merits of a total gastrectomy and an esophagectomy from prospectively collected data from the Dutch Upper GI Cancer Audit combined with survival data from the Dutch national insurance database. It was found that there was no significant difference in postoperative morbidity, mortality, radicality, lymph node yield nor survival. This study was unable to determine one procedure to be superior, leading us to the only objectively possible advice that the choice should be made based on the surgeon's experience and keeping the quality of life of the patient in mind, pending further research.

If the malignancy is located in the mid to distal esophagus and it is possible to resect with curative intent, surgical treatment should include an esophagectomy including the resection of the affected part of the esophagus and the gastro-esophageal junction. This leaves the patient without a tract that can transport oral intake to the intestine. The distance cannot be made up by simply pulling the stomach up to the resection line, since the stomach and attached intestine are firmly attached in the abdomen. Although there are several methods that can be chosen to bridge this gap, in general the preferred approach is a gastric tube reconstruction.

When a patient is eligible for an esophagectomy, there is still the matter of the surgical approach to consider. These resections can be performed through an open surgical approach, laparoscopic and robotic assisted. In addition to these options, there is the choice between a transhiatal or transthoracic approach. A transhiatal resection spares the patient a thoracic phase, meaning that the thorax will be left relatively undisturbed. The esophagus is mobilized through the diaphragmatic hiatus, and the anastomosis with the gastric tube is performed through a cervical incision. This has the advantage of relatively little tissue damage in the thorax, but does mean that a less extended lymphadenectomy is performed. A transthoracic resection can be performed in several ways. The major variations used in the Netherlands are the McKeown and Ivor Lewis procedures. A McKeown esophageal resection is also known as a 3-stage resection, since it includes an abdominal, thoracic and cervical phase. The esophagus is mobilized abdominally, thoracically and the anastomosis is made through a cervical incision. This resection has the advantage of a maximum removal of esophageal tissue, but also leads to the greatest disturbance of normal anatomy. An Ivor Lewis, or 2-stage, resection only has an abdominal and thoracic

phase. The anastomosis is made in the intrathoracically. Therefore, this variation cannot be performed when the tumor is located in the proximal part the esophagus.

The transthoracic esophagectomy is known for its more radical resection due to the en-bloc resection of the affected esophagus with an extensive intrathoracic lymph node dissection^{29,30}, compared to the more limited lymph node dissection in the transhiatal approach³¹. Research has thus far not been able to determine the clear superiority of one of these approaches. Although the transthoracic approach provides a superior oncologic resection in terms of a higher lymph node yield, the transhiatal procedure is associated with shorter hospital stay and decreased short term mortality and morbidity³²⁻³⁵.

Recent research suggests a link between a higher lymph node yield and long-term survival^{36,37}, although there are several conflicting publications on this subject^{33,38-42}. Chapter 10 describes a retrospective analysis of audit data, and reaffirms the existing knowledge that a transhiatal resection is safer in the short term, but a transthoracic resection allows for a more extensive resection of lymph nodes. As lymph nodes are an important part of staging, and therefore determining the prognosis of the patient, this would be an argument for excising as much relevant tissue as possible. However, this does come at the cost of increased short-term morbidity and short-term mortality.

Patients frequently have short term functional complaints of the gastric conduit. All types of reconstruction can lead to side-effects such as for example diarrhea, reflux, dumping, thoracic stomach syndrome and delayed gastric emptying. There are several studies that describe treatment or prevention, but none of these try to identify and treat the condition before the first outpatient visit. Common preventative measures are taken during the creation of the gastric tube. These measures include pyloromyotomies, digital pyloric fracture and injections with botox. These procedures can also performed as a treatment when symptoms arise postoperatively, but that means that the patient requires a second intervention. Chapter 9 describes a prospective case series that aimed to identify delayed gastric tube emptying early, and attempt treatment during the same hospitalization as the esophagectomy. Based on several criteria, the study attempted to identify this condition as soon as possible and initiate treatment as soon as feasible. In this study, that meant that any patient with symptoms fitting delayed gastric emptying at day 8-10 postoperatively was scheduled for a therapeutic esophagogastroscopy, where the pyloric sphincter was expanded using a balloon. This is a known safe and relatively easy procedure that has been shown to be effective, although repeat dilations are often needed. In the cohort of twelve patients this treatment was immediately effective in seven patients matching the definition of success: meaning patients could expand oral intake starting on the same day as the procedure. The other patients were all able

to expand their oral intake soon after. Three months postoperatively all patients had at least partial intake, with just four needing supplemental nightly gavage feeding through a jejunostomy tube. At six months postoperatively all patients were able to attain their full desired caloric intake orally.

Treating symptoms early, instead of waiting for them to naturally resolve, can be part of an approach that is geared more towards quality of life. These patients would otherwise have spent a significant time with a nil-per-mouth regime and gavage feeding, with accompanying nausea and lack of appetite. As none of the patients in our study experienced complications, and as there is no evidence of significant dilation-related morbidity this will remain part of the standard treatment protocol.

This thesis has shown that immense progress has been made on various aspects of the surgical treatment of both benign and malignant upper GI disease. With great effort of clinicians, researchers and patients, research performed in the past decades has not only led to improvements in the accuracy of diagnosing disease, but has also improved on the methods for selecting the optimal treatment modality and surgical approach. The trend towards increased sharing of research data and the advent of national registries have allowed researchers to perform studies with less resources and with a larger number of patients than ever before.

In the future, technological advancement is expected to continue to improve the outcomes of surgery. Newer techniques such as near-infrared fluorescence allow clinicians – among other applications - to see the transport of a fluid in a living body, allowing real-time insights in vascularization of tissue. This visualization enables surgeons to judge the viability of tissue during surgery, and is gaining popularity in for example gastric tube surgery where it is essential that the edges of the sutured tissue have sufficient blood supply to avoid necrosis and resulting leakage. These techniques can also be combined with for example robotic assistance, allowing surgeons to operate extremely precisely and at the same time being able to judge the viability of an anastomosis. Although short- and long-term outcomes remain important, the large body of research into postoperative quality of life shows that this is becoming a larger factor in medicine. Great efforts are being made to individualize treatment for both benign and malignant disease. The advances in (neo)adjuvant therapy have led to highly personalized medicine, and improvements in this area will hopefully lead to a smaller number of patients requiring surgery.

The significant advances in modern medicine described in this thesis make it clear that surgical care has advanced enough that we can start to divide the medical focus between curation and quality of life. While there are still definite gains to be made in curative care, survival rates have been going up, while complications and short-term mortality have been decreasing and continue to do so. Whether it is the

often-ignored splenic infarctions, recurrent hiatal hernia with invalidating reflux, or an older patient that might not be best served by a potentially curative resection, these secondary outcomes are very important to the individual patient and should be the subject of future research. Choosing the best treatment path should always be done with the patient and in this context.

REFERENCES

1. Oelschläger BK, Pellegrini CA, Hunter J, et al. Biologic Prosthesis Reduces Recurrence After Laparoscopic Paraesophageal Hernia Repair. *Trans . Meet Am Surg Assoc.* 2006;124:146–55.
2. Sathasivam R, Bussa G, Viswanath Y, et al. ‘Mesh hiatal hernioplasty’ versus ‘suture cruroplasty’ in laparoscopic para-oesophageal hernia surgery; a systematic review and meta-analysis. *Asian J Surg.* 2019 Jan;42(1):53–60.
3. Asti E, Lovece A, Bonavina L, et al. Laparoscopic management of large hiatus hernia: five-year cohort study and comparison of mesh-augmented versus standard crura repair. *Surg Endosc.* 2016 Dec 29;30(12):5404–9.
4. Zhang C, Liu D, Li F, et al. Systematic review and meta-analysis of laparoscopic mesh versus suture repair of hiatus hernia: objective and subjective outcomes. *Surg Endosc.* 2017 Dec;31(12):4913–22.
5. Dunne N, Stratford J, Jones L, et al. Anatomical failure following laparoscopic antireflux surgery (LARS): does it really matter? *Ann R Coll Surg Engl.* 2010 Mar;92(2):131–5.
6. Donkervoort SC, Bais JE, Rijnhart-de Jong H, et al. Impact of anatomical wrap position on the outcome of Nissen fundoplication. *Br J Surg.* 2003 Jul;90(7):854–9.
7. Robinson B, Dunst CM, Cassera MA, et al. 20 years later: laparoscopic fundoplication durability. *Surg Endosc.* 2015 Sep 9;29(9):2520–4.
8. Luketich JD, Nason KS, Christie NA, et al. Outcomes after a decade of laparoscopic giant paraesophageal hernia repair. *J Thorac Cardiovasc Surg.* 2010 Feb;139(2):395–404, 404.e1.
9. Banki F, Kaushik C, Roife D, et al. Laparoscopic Repair of Large Hiatal Hernia Without the Need for Esophageal Lengthening With Low Morbidity and Rare Symptomatic Recurrence. *Semin Thorac Cardiovasc Surg.* 2017;29(3):418–25.
10. Gehrig T, Mehrabi A, Fischer L, et al. Robotic-assisted paraesophageal hernia repair—a case-control study. *Langenbeck’s Arch Surg.* 2013 Jun;398(5):691–6.
11. Brenkman HJF, Parry K, van Hillegersberg R, et al. Robot-Assisted Laparoscopic Hiatal Hernia Repair: Promising Anatomical and Functional Results. *J Laparoendosc Adv Surg Tech.* 2016 Jun;26(6):465–9.
12. Tolboom RC, Draaisma WA, Broeders IAMJ. Evaluation of conventional laparoscopic versus robot-assisted laparoscopic redo hiatal hernia and antireflux surgery: a cohort study. *J Robot Surg.* 2016;10(1):33–9.
13. Müller-Stich BP, Reiter MA, Mehrabi A, et al. No relevant difference in quality of life and functional outcome at 12 months’ follow-up—a randomised controlled trial comparing robot-assisted versus conventional laparoscopic Nissen fundoplication. *Langenbeck’s Arch Surg.* 2009 May 23;394(3):441–6.
14. Falkenback D, Lehane CW, Lord RVN. Robot-assisted oesophageal and gastric surgery for benign disease: Antireflux operations and Heller’s myotomy. *ANZ J Surg.* 2015;85(3):113–20.
15. Galvani CA, Loebel H, Osuchukwu O, et al. Robotic-Assisted Paraesophageal Hernia Repair: Initial Experience at a Single Institution. *J Laparoendosc Adv Surg Tech.* 2016 Apr;26(4):290–5.

16. Draaisma W, Gooszen H, Consten E, et al. Mid-term results of robot-assisted laparoscopic repair of large hiatal hernia: a symptomatic and radiological prospective cohort study. *Surg Technol Int*. 2008;(17):165–70.
17. Hanly EJ, Talamini MA. Robotic abdominal surgery. *Am J Surg*. 2004 Oct;188(4A Suppl):19S–26S.
18. Braumann C, Jacobi CA, Menenakos C, et al. Robotic-assisted laparoscopic and thoracoscopic surgery with the da Vinci system: a 4-year experience in a single institution. *Surg Laparosc Endosc Percutan Tech*. 2008 Jun;18(3):260–6.
19. Broeders IAMJ. Robotics: The next step? *Best Pract Res Clin Gastroenterol*. 2014;28(1):225–32.
20. Blomqvist a, Dalenbäck J, Hagedorn C, et al. Impact of complete gastric fundus mobilization on outcome after laparoscopic total fundoplication. *J Gastrointest Surg*. 2000;4(5):493–500.
21. O’Boyle CJ, Watson DI, DeBeaux a C, et al. Preoperative prediction of long-term outcome following laparoscopic fundoplication. *ANZ J Surg*. 2002 Jul;72(7):471–5.
22. Watson DI, Pike GK, Baigrie RJ, et al. Prospective double-blind randomized trial of laparoscopic Nissen fundoplication with division and without division of short gastric vessels. *Ann Surg*. 1997;226(5):642–52.
23. Khatri K, Sajid MS, Brodrick R, et al. Laparoscopic Nissen fundoplication with or without short gastric vessel division: A meta-analysis. *Surg Endosc Other Interv Tech*. 2012;26(4):970–8.
24. Luostarinen ME, Isolauri JO. Randomized trial to study the effect of fundic mobilization on long-term results of Nissen fundoplication. *Br J Surg*. 1999;86(5):614–8.
25. Kosek V, Wykypiel H, Weiss H, et al. Division of the short gastric vessels during laparoscopic Nissen fundoplication: Clinical and functional outcome during long-term follow-up in a prospectively randomized trial. *Surg Endosc Other Interv Tech*. 2009;23(10):2208–13.
26. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015 Mar;65(2):87–108.
27. IKNL. Nederlandse Kankerregistratie (NKR). [cited 2018 Nov 20]. Available from: <https://www.cijfersoverkanker.nl>
28. GLOBOCAN 2012 (IARC). Estimated Incidence, Mortality and Prevalence Worldwide in 2012. Estimated Incidence, Mortality and Prevalence Worldwide in 2012. [cited 2017 Aug 1]. Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx?cancer=stomach
29. McKeown KC. Total three-stage oesophagectomy for cancer of the oesophagus. *Br J Surg*. 1976 Apr;63(4):259–62.
30. Lewis I. The surgical treatment of carcinoma of the oesophagus; with special reference to a new operation for growths of the middle third. *Br J Surg*. 1946 Jul;34:18–31.
31. Orringer MB, Sloan H. Esophagectomy without thoracotomy. *J Thorac Cardiovasc Surg*. 1978 Nov;76(5):643–54.
32. Hulscher JBF, Van Sandick JW, De Boer AGEM, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. *N Engl J Med*. 2002;347(21):1662–9.

33. Boshier PR, Anderson O, Hanna GB. Transthoracic versus transhiatal esophagectomy for the treatment of esophagogastric cancer: A meta-analysis. *Ann Surg.* 2011;254(6):894–906.
34. Wolff CS, Castillo SF, Larson DR, et al. Ivor Lewis approach is superior to transhiatal approach in retrieval of lymph nodes at esophagectomy. *Dis Esophagus.* 2008;21(4):328–33.
35. van der Werf LR, Dikken JL, van Berge Henegouwen MI, et al. A Population-based Study on Lymph Node Retrieval in Patients with Esophageal Cancer: Results from the Dutch Upper Gastrointestinal Cancer Audit. *Ann Surg Oncol.* 2018;25(5):1211–20.
36. Visser E, Rossum PSNV, Ruurda JP, et al. Impact of Lymph Node Yield on Overall Survival in Patients Treated with Neoadjuvant Chemoradiotherapy Followed by Esophagectomy for Cancer. *Ann Surg.* 2017;266(5):863–9.
37. Rizzetto C, DeMeester SR, Hagen JA, et al. En bloc esophagectomy reduces local recurrence and improves survival compared with transhiatal resection after neoadjuvant therapy for esophageal adenocarcinoma. *J Thorac Cardiovasc Surg.* 2008;135(6):1228–36.
38. Gockel I, Heckhoff S, Messow CM, et al. Transhiatal and transthoracic resection in adenocarcinoma of the esophagus: Does the operative approach have an influence on the long-term prognosis? *World J Surg Oncol.* 2005;3:1–11.
39. Grotenhuis BA, Van Heijl M, Zehetner J, et al. Surgical management of submucosal esophageal cancer: Extended or regional lymphadenectomy? *Ann Surg.* 2010;252(5):823–9.
40. Ovrebo KK, Lie SA, Laerum OD, et al. Long-term survival from adenocarcinoma of the esophagus after transthoracic and transhiatal esophagectomy. *World J Surg Oncol.* 2012;10:1–10.
41. Davies AR, Sandhu H, Pillai A, et al. Surgical resection strategy and the influence of radicality on outcomes in oesophageal cancer. *Br J Surg.* 2014;101(5):511–7.
42. Omloo JMT, Lagarde SM, Hulscher JBF, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. *Ann Surg.* 2007 Dec;246(6):992–1000; discussion 1000-1.

APPENDICES

The background of the page is an abstract composition of geometric shapes. It features a dark, almost black, angular shape on the left side that meets a lighter, grayish-blue area. A prominent vertical line runs down the right side of the page. The overall aesthetic is minimalist and architectural.

APPENDIX I

Summary in Dutch /
Nederlandse samenvatting



INTRODUCTIE

Dit proefschrift beschrijft onderzoeken waarin ontwikkelingen in slokdarm- en maagchirurgie worden onderzocht. Het proefschrift bestaat uit twee delen, ingedeeld op benigne en maligne aandoeningen. Het eerste deel beschrijft de behandeling en diagnostiek van refluxziekte, waarbij het tweede deel op maligne aandoeningen zoals slokdarm- en maagkanker in gaat.

Gedurende de laatste eeuw is de chirurgische behandeling van deze aandoeningen ontwikkeld van open chirurgie met bijbehorende mortaliteit naar kijkoperaties en in sommige gevallen zelfs robot-geassisteerde procedures. Deze vooruitgang is niet zonder slag of stoot bereikt. De eerste kijkoperaties hadden een beduidend hoger risico op ernstige complicaties in vergelijking met open chirurgie, maar mettertijd is zoveel vooruitgang geboekt dat deze modernere techniek dat tegenwoordig in bijna alle gevallen kijkoperaties de voorkeur hebben boven een traditionele operatie.

De traditionele, open, chirurgische procedure geeft de chirurg directe toegang tot het weefsel, en geeft door middel van tast een uitstekend gevoel voor hoe de anatomie in elkaar steekt. Deze manier van opereren leidt echter tot veel weefselschade en verlittekening. Zeker bij problemen die zich niet op een eenvoudig bereikbare plaats in het lichaam afspelen, is het veelal lastig om voldoende toegang tot het operatiegebied te verkrijgen zonder veel schade aan te richten. Bovendien vereist een open chirurgische operatie een grote incisie. Kijkoperaties lossen een deel van dit probleem op. Een deel van deze problemen kan opgelost worden middels een kijkoperatie. Hierbij is het mogelijk om via kleine incisies, weinig meer dan steekopeningen, toegang te krijgen tot het operatiegebied. Doordat de instrumenten erg klein zijn, is het mogelijk om zeer precies te werken. Door deze precisie treedt er ook minder weefselschade en verlittekening op.

Ondanks de voordelen van kijkoperaties, kleven er ook nadelen aan deze manier van opereren. Een nadeel van kijkoperaties is bijvoorbeeld dat er lange tijd nodig is om voldoende gewend te raken aan het hefboomeffect van de instrumenten: de instrumenten scharnieren op de insteekopening, waardoor een kleine beweging buiten het lichaam in vrijwel alle gevallen leidt tot een kleinere of grotere beweging van het instrument in het lichaam. Daarnaast zijn deze instrumenten star.

Deze nadelen kunnen grotendeels worden weggenomen door middel van robot-geassisteerde chirurgie. Robotische instrumenten hebben veelal pols-achtige gewrichten aan het uiteinde, waardoor grote precisie mogelijk is. Het nadeel van robot-geassisteerde chirurgie is het gebrek aan tactiele feedback, naast onder andere hogere kosten en een veelal langere operatietijd. Op dit moment zitten we in de fase waarin robot-geassisteerde chirurgie en andere moderne technieken qua

uitkomsten veelal minstens equivalent zijn aan kijkoperaties, en kijken we steeds meer naar de voordelen van robot-geassisteerde chirurgie ten opzichte van andere operatiemethoden. Naast deze technologische ontwikkeling van chirurgische methoden is de aandacht tijdens een chirurgische behandeling ook aan het verschuiven van het verhelpen van de pathologie naar een bredere blik waarbij ook de kwaliteit van leven in overweging wordt genomen. In sommige gevallen leidt dit zelfs tot de keuze om niet te behandelen.

BENIGNE AANDOENINGEN

Het eerste deel van dit proefschrift focust zich op een benigne aandoening: middenrifbreuken. Dit ziektebeeld wordt gekenmerkt door de aanwezigheid van maagzuur in de slokdarm (gastro-oesofageale refluxziekte), en kan leiden tot symptomen zoals zuurbranden, misselijkheid, en oprispingen. In ernstige gevallen is er zelfs sprake van slikklachten, aantasting van het gebit en is er een verhoogd risico op kanker. In sommige gevallen is medicamenteuze of gastroscopische behandeling van reflux niet effectief genoeg, en kan chirurgisch of endoscopisch ingrijpen worden overwogen. De onderzoeken in dit deel van het proefschrift richten zich met name op de behandeling van een van de oorzaken van refluxziekte: middenrifbreuken.

MIDDENRIFBREUKEN (HERNIA DIAFRAGMATICA)

In de normale anatomische situatie lijnt het laatste deel van de slokdarm, vlak voordat deze overgaat in de maag, op met het middenrif. In dit laatste deel van de slokdarm bevindt zich de onderste slokdarmkringspier (Lower Esophageal Sphincter, LES): een kringspier die ontspant wanneer dat gewenst is, en in alle andere gevallen de inhoud van de maag uit de slokdarm weert. Deze kringspier wordt normaal gesproken ondersteund door druk van buiten de slokdarm, geleverd door het middenrif. In het geval van een middenrifbreuk is de aansluiting van het middenrif op de kringspier echter verstoord. Dit kan gebeuren doordat de slokdarm door de opening in het middenrif schuift, er weefsel zoals (een deel van) de maag, vet of darmen langs de slokdarm heen door de opening richting de borstkas schuiven, of een combinatie hiervan. Vanwege deze variatie in anatomische afwijkingen is er ook een spectrum aan mogelijke klachten die hieruit voortvloeien, variërend van passageklachten tot terugstromen van maagzuur of zelfs voedsel.

Het is niet exact bekend hoeveel mensen een middenrifbreuk hebben, aangezien een deel van de mensen met deze afwijking geen klachten hebben. Van de mensen met klachten is een groot aantal geholpen met medicatie zoals maagzuurremmers. De groep die niet voldoende heeft aan medicatie kan deels kan geholpen worden door een ingreep via de slokdarm, maar een deel heeft hier ook niet voldoende aan en komt dan bij de chirurg terecht. Deze patiënten hebben vaak ernstige aanhoudende klachten en in zeldzame gevallen beschadiging van de slokdarm of erger.

BEHANDELING

Zoals eerder beschreven gaat het bij een middenrifbreuk om benigne pathologie. Het gaat om een relatief onschadelijke aandoening met een lage kans op ernstigere afwijkingen zoals kanker. De last voor de patiënt uit zich vooral in een verlaagde kwaliteit van leven door de zojuist beschreven symptomen. Een behandeling voor middenrifbreuken moet dan ook bijzonder veilig zijn: de behandeling mag immers niet schadelijker zijn dan de kwaal. Met deze argumentatie zou operatief ingrijpen een van de laatste oplossingsrichtingen moeten zijn. Een patiënt die nog geen minder ingrijpende behandeling zoals medicatie of scopisch ingrijpen overwogen heeft, komt dan ook maar zeer zelden in aanmerking voor een operatie. Zelfs in situaties waarin alle overige oplossingsrichtingen onvoldoende resultaat geboden hebben kan het beter zijn om niet te opereren, zoals bijvoorbeeld in het geval van milde nachtelijke klachten van zuurbranden als enige symptoom. Deze klacht zal bijvoorbeeld met aan zekerheid grenzende waarschijnlijkheid niet leiden tot overlijden, maar een operatie is nooit zonder risico op sterfte. In het geval van een middenrifbreuk met zodanige symptomen dat de patiënt bij de chirurg op het spreekuur verschijnt zijn andere opties meestal al geprobeerd en is opereren vaak de enige geschikte behandeling¹.

De operatiemethode die de voorkeur geniet bij een middenrifbreuk heet een funduplicatie. Tijdens deze operatie wordt grofweg de fundus van de maag om de slokdarm gevouwen en vastgehecht. Daarnaast wordt indien nodig de opening in het middenrif verkleind. Het effect van deze procedure is tweeledig: de LES wordt ondersteund door de druk van buitenaf, en de funduplicatie vormt een weefselmassa die lastiger opnieuw door het middenrif kan migreren. Er is erg veel variatie mogelijk in de exacte uitvoering van deze ingreep, met de bijbehorende variatie in uitkomsten. Over het algemeen genomen is deze operatie met 90% kans op succes erg effectief, en er treden maar weinig complicaties op indien de operatie wordt uitgevoerd in een centrum met voldoende ervaring²⁻⁷.

Helaas is het ondanks de vooruitgang van de afgelopen decennia nog altijd gebruikelijk dat een patiënt opnieuw een middenrifbreuk oploopt. Verschillende studies rapporteren een recidiefkans van 40%⁸⁻¹¹, meestal binnen de eerste vijf jaar na de initiële operatie^{1,12}. Een recidief wil overigens niet altijd zeggen dat de patiënt ook klachten ontwikkelt: een asymptomatisch recidief is meer regel dan uitzondering^{13,14}. Wanneer de klachten zodanig zijn dat een heroperatie wel overwogen moet worden is succes niet gegarandeerd. Helaas is opnieuw opereren vele malen lastiger dan de eerste keer, vooral vanwege verklevingen en de veranderde anatomie. De tevredenheid van patiënten neemt af naarmate er vaker ingegrepen wordt, en de risico's nemen toe^{6,15,16}.

MALIGNE AANDOENINGEN

Het tweede deel van dit proefschrift bevat studies naar kanker van de slokdarm en de slokdarm-maagovergang. Slokdarmkanker staat op de achtste plaats van meest voorkomende kwaadaardigheden ter wereld. In tegenstelling tot reflux en middenrifbreuken is dit een bijzonder gevaarlijke aandoening met een vijfjaarsoverleving van slechts rond de 20%^{17,18}. Hoewel de behandeling van slokdarm sterk verbeterd is met neoadjuvante behandelingen is (extreem vroege stadia van de aandoening daar gelaten) chirurgie nog altijd de enige manier om genezing te bereiken¹⁹.

De operatieve mogelijkheden voor slokdarmkanker hangen sterk af van de locatie van de afwijking. Aangezien de slokdarm aan beide uiteinden relatief verankerd is, is het niet mogelijk om eenvoudigweg een stuk te verwijderen en de losse einden aan elkaar te hechten. Afhankelijk van hoeveel van de slokdarm of zelfs maag er verwijderd moet worden, kan de aansluiting van de resectievlakken in de hals of borstholte gemaakt worden. Grofweg zijn er twee routes om deze operatie uit te voeren: via de borstholte of via de buikholte.

Bij een operatie via de borstholte is er voor de chirurg relatief veel vrijheid voor wat betreft het deel van de slokdarm dat verwijderd wordt. Een voordeel van deze benadering is de uitgebreide mogelijkheid om lymfeklieren rondom de tumor te verwijderen, aangezien dit vaak de eerste plaats is waar uitzaaiingen optreden. Ook is het mogelijk om optisch te inspecteren hoe de omgeving van de tumor er uit ziet. Het nadeel van deze methode is dat er relatief veel weefselschade optreedt. Een alternatief is een operatie via de buikholte. Hierbij wordt de slokdarm relatief dicht bij de maag doorgenomen (of wordt zelfs een deel van de maag verwijderd), en wordt de slokdarm via een incisie in de hals doorgenomen en verwijderd. Een operatie via de buikholte wordt over het algemeen beschouwd als een minder zware operatie, echter gaat dit ten koste van bijvoorbeeld een uitgebreidere verwijdering van lymfweefsel. Op basis van de huidige literatuur is niet zonder meer uitsluitel te geven over de voorkeursmethode, aangezien er een grote variëteit in patiëntpopulaties en operatietechnieken beschreven wordt met wisselende uitkomsten.

Wanneer de te overbruggen afstand te groot is, zijn er verschillende opties om met een interponaat toch tot een continue kanaal te komen. De meest frequent gebruikte methode is de constructie van een buismaag: hierbij wordt de maag omgevormd tot een langere buis, en wordt deze aangesloten op de slokdarm. Alternatieven zijn bijvoorbeeld het gebruik van een stuk dikke darm. Bij beide opties is het een uitdaging om de doorbloeding van het interponaat te garanderen. Zowel de maag als darm zitten onder andere met bloedvaten verankerd aan de omringende weefsels. Een deel hiervan moet worden doorgenomen om het orgaan te kunnen

verplaatsen naar de nieuwe locatie, met als gevolg dat de doorbloeding in vrijwel alle gevallen verminderd. Aangezien onvoldoende doorbloed weefsel afsterft, is dit een veelvoorkomende oorzaak van complicaties zoals naadlekkages en perforaties.

In Nederland wordt in het algemeen gekozen voor chemotherapie plus bestraling¹⁹ indien de aandoening te genezen is. Dit wordt bepaald op basis van bijvoorbeeld de risicofactoren zoals ingroei in omliggende weefsels, grootte van de tumor en uitzaaiing. Ondanks deze weinig hoopvolle feiten is de afgelopen 30 jaar de vijfjaarsoverleving bepaalde maligniteiten (niet-uitgezaaid adenocarcinoom) van de slokdarm gestegen van 12% naar 47% in 2015²⁰. Onder meer omdat er geen sluitend bewijs is voor de beste behandelmethodede voor wat betreft de beste kans op overleving, is kwaliteit van leven na de operatie een belangrijke factor bij het bepalen van het behandeltraject. Het vinden van de optimale balans tussen maximale resectie van de tumor en het behoud van de hoogst haalbare kwaliteit van leven is hierdoor een van de belangrijkste doelen in de besluitvorming.

HET PROEFSCHRIFT

In hoofdstuk 5 van dit proefschrift worden de veiligheid en risico's van middenrifchirurgie beschreven. Iedere operatie, hoe zorgvuldig uitgevoerd deze ook mag zijn, draagt risico's met zich mee. Zeker in het geval van benigne aandoeningen, die in verreweg de meeste gevallen geen significante invloed hebben op de overleving, dienen deze risico's minimaal te zijn. Deze studie toont aan dat complexe middenrifchirurgie in een centrum met veel ervaring lage risico's met zich meebrengt. Hoofdstuk 2 bevat een discussie en handvaten voor chirurgen voor wanneer een anti-reflux-operatie wel tot complicaties leidt. Er wordt zowel op complicaties tijdens de operatie als ongewenste resultaten na de operatie in gegaan. Wanneer anti-reflux chirurgie tot een goed resultaat leidt, is dit helaas vaak niet voor de rest van het leven van de patiënt. Hoofdstuk 3 gaat over de besluitvorming in het geval van een recidief middenrifbreuk. Er wordt beschreven hoe een heroperatie het beste uitgevoerd kan worden, maar ook wanneer opereren wellicht niet tot een verbetering van de situatie zal leiden. In deze gevallen is het soms beter om in dialoog met de patiënt te besluiten om niet in te grijpen en te zoeken naar niet-operatieve mogelijkheden om de klachten te verminderen.

Tijdens anti-refluxoperaties moet in veel gevallen de maag losgemaakt worden van omringend weefsel om de maag om de slokdarm te kunnen vouwen (funduplicatie). Hierbij worden veelal de vaten tussen de milt en de maag doorgenomen: de vasa brevia. Het is onvoldoende onderzocht of dit ongewenste effecten kan hebben, hoewel er een aantal rapportages zijn van infarcten in de milt na deze ingreep, die kunnen leiden tot bijvoorbeeld abcesvorming. In hoofdstuk 4 wordt een pilotstudie beschreven, waarin onderzocht is of het mogelijk is om met fluorescentie tijdens

de operatie te detecteren of de doorbloeding van de milt verminderd wordt na het doornemen van deze vaten. Het blijkt dat bij twee van de tien patiënten duidelijk verminderde doorbloeding van de milt te zien is na het doornemen van de vasa brevia, wat leidt tot de conclusie dat een groter onderzoek gerechtvaardigd lijkt.

Een van de veelgehoorde kritieken op robot-geassisteerde chirurgie is de hogere kosten. Een belangrijk deel van de kosten van een operatie zijn de kosten voor het gebruik van een operatiekamer, waardoor de duur van een operatie een van de belangrijkste aandelen in de kosten van een operatie vormt. Hoofdstuk 6 beschrijft een studie die als doel heeft te beoordelen of gerapporteerde operatietijden adequaat berekend zijn. De studie onderzoekt of er sprake is van mogelijke tekortkomingen en schetst richtlijnen voor het accuraat beschrijven van deze tijden in toekomstige studies. De studie onderzoekt de vastlegging van operatietijden van de operatieassistent en anesthesioloog, en vergeleek dit met de werkelijke tijden zoals geobserveerd door een onderzoeker. De studie concludeert dat de geregistreerde tijden flink van elkaar verschillen, waardoor het doen van objectieve uitspraken over de duur van een operatie niet zonder meer mogelijk is. Ook beschrijft dit hoofdstuk een literatuurstudie naar de rapportage van operatietijden zoals waarop de kostenanalyse van robotchirurgie vaak gebaseerd wordt, en wordt geconcludeerd dat artikelen vaak niet voldoende details over hun meetmethoden geven om een onderbouwd oordeel te kunnen vellen.

In hoofdstuk 7 wordt onderzocht of het voor de chirurg mogelijk is om de oorzaak van teruggekeerde klachten na anti-refluxchirurgie te achterhalen middels alleen een CT-scan. Soms is de oorzaak terug te leiden tot een recidief middenrifbreuk, maar het gebeurt ook dat patiënten klachten ontwikkelen doordat hechtingen te strak zitten of deze juist los zijn gekomen. Deze studie onderzoekt het nut van een CT-scan bij patiënten die een tweede keer zijn geopereerd. De CT-scans die bij deze patiënten zijn gemaakt, zijn opnieuw beoordeeld door zowel chirurgen en radiologen. De studie concludeert dat er vaak meerdere onderzoeksmethoden nodig zijn om tot een volledig beeld van de oorzaak te komen.

In deel 2 van het proefschrift worden onderzoeken naar de behandeling van maag- en slokdarmkanker beschreven.

De reden dat deze twee ogenschijnlijk verschillende soorten maligniteiten beiden ter sprake komen, is omdat het in de praktijk soms lastig is om te bepalen of een tumor zich in de slokdarm, maag of precies op de overgang bevindt. In hoofdstuk 11 wordt middels een nationale onderzoeksdatabase onderzocht of tumoren op de overgang tussen slokdarm en maag beter behandeld kunnen worden door de maag en een stuk slokdarm te verwijderen, of door de focus van resectie meer op de slokdarm te leggen. De studie concludeert dat de resultaten van beide methoden

relatief vergelijkbaar zijn wanneer een tumor voor beide methoden in aanmerking komt, en de keuze vooral bepaald zou moeten worden op basis van de ervaring van het behandelteam en de kwaliteit van leven van de patiënt. Hoofdstuk 10 vergelijkt of een tumor van de slokdarm waarbij zowel een benadering via de borst- als buikholte in aanmerking komen, welke van deze twee opties leidt tot betere uitkomsten op de korte termijn. Ook deze studie is uitgevoerd met data uit een nationale onderzoeksdatabase. De studie concludeert dat een behandeling via de borstholte leidt tot een uitgebreidere verwijdering van lymfeweefsel, ten koste van verhoogde sterfte op de korte termijn en complicaties. De winst van een benadering via de borstholte ligt op basis van ander onderzoek waarschijnlijk in een hogere overleving op de lange termijn, aangezien er bij een benadering via de buik mogelijk lymfeklieren met metastasen achter blijven.

In hoofdstuk 8 wordt onderzocht hoeveel risico een patiënt loopt bij de operatieve behandeling van maagkanker, waarbij de focus ligt op de leeftijd van de patiënt.

Nadat (een deel van) de slokdarm verwijderd is, wordt vaak een buismaag gebruikt om continuïteit van het maag-darmkanaal te herstellen. Een van de veelvoorkomende complicaties van deze operatie is een vertraagde ontleding van de buismaag. Dit houdt in dat voedsel niet voldoende snel uit de buismaag geëvacueerd wordt richting de darm. Een mogelijke behandeling van dit probleem is een dilatatie van de pylorus: de sluitspier van de maag. Hoofdstuk 9 beschrijft een pilotstudie waarin deze sluitspier middels een gastroscopie met een ballon wordt opgeblazen om deze te verwijderen, bij patiënten die zeer vroeg na de operatie al last hebben van vertraagde ontleding van de buismaag. De conclusie van deze studie is dat deze methode veilig en effectief lijkt te zijn, en dat een grotere studie op basis van deze resultaten gerechtvaardigd lijkt.

REFERENTIES

1. Stefanidis D, Hope WW, Kohn GP, Reardon PR, Richardson WS, Fanelli RD (2010) Guidelines for surgical treatment of gastroesophageal reflux disease. *Surg Endosc* 24:2647–2669
2. Robinson B, Dunst CM, Cassera MA, Reavis KM, Sharata A, Swanstrom LL (2015) 20 years later: laparoscopic fundoplication durability. *Surg Endosc* 29:2520–4
3. Luketich JD, Nason KS, Christie NA, Pennathur A, Jobe BA, Landreneau RJ, Schuchert MJ (2010) Outcomes after a decade of laparoscopic giant paraesophageal hernia repair. *J Thorac Cardiovasc Surg* 139:395–404, 404.e1
4. Banki F, Kaushik C, Roife D, Mitchell KG, Miller CC (2017) Laparoscopic Repair of Large Hiatal Hernia Without the Need for Esophageal Lengthening With Low Morbidity and Rare Symptomatic Recurrence. *Semin Thorac Cardiovasc Surg* 29:418–425
5. Tolboom R, Broeders I, Draaisma W (2015) Robot-assisted laparoscopic hiatal hernia and antireflux surgery. *J Surg Oncol* 112:266–270
6. Mertens AC, Tolboom RC, Zavrtnik H, Draaisma WA, Broeders IAMJ (2019) Morbidity and mortality in complex robot-assisted hiatal hernia surgery: 7-year experience in a high-volume center. *Surg Endosc* 33:2152–2161
7. Tolboom RC, Draaisma WA, Broeders IAMJ (2016) Evaluation of conventional laparoscopic versus robot-assisted laparoscopic redo hiatal hernia and antireflux surgery: a cohort study. *J Robot Surg* 10:33–39
8. Oelschläger BK, Pellegrini CA, Hunter J, Soper N, Brunt M, Sheppard B, Jobe B, Polissar N, Mitsumori L, Nelson J, Swanstrom L (2006) Biologic Prosthesis Reduces Recurrence After Laparoscopic Paraesophageal Hernia Repair. *Trans. Meet Am Surg Assoc* 124:146–155
9. Sathasivam R, Bussa G, Viswanath Y, Obuobi R-B, Gill T, Reddy A, Shanmugam V, Gilliam A, Thambi P (2019) ‘Mesh hiatal hernioplasty’ versus ‘suture cruroplasty’ in laparoscopic paraesophageal hernia surgery; a systematic review and meta-analysis. *Asian J Surg* 42:53–60
10. Asti E, Lovece A, Bonavina L, Milito P, Sironi A, Bonitta G, Siboni S (2016) Laparoscopic management of large hiatus hernia: five-year cohort study and comparison of mesh-augmented versus standard crura repair. *Surg Endosc* 30:5404–5409
11. Zhang C, Liu D, Li F, Watson DJ, Gao X, Koetje JH, Luo T, Yan C, Du X, Wang Z (2017) Systematic review and meta-analysis of laparoscopic mesh versus suture repair of hiatus hernia: objective and subjective outcomes. *Surg Endosc* 31:4913–4922
12. Mittal SK, Bikhchandani J, Gurney O, Yano F, Lee T (2011) Outcomes after repair of the intrathoracic stomach: objective follow-up of up to 5 years. *Surg Endosc* 25:556–566
13. Dunne N, Stratford J, Jones L, Sohampal J, Robertson R, Booth MI, Dehn TCB (2010) Anatomical failure following laparoscopic antireflux surgery (LARS): does it really matter? *Ann R Coll Surg Engl* 92:131–5
14. Donkervoort SC, Bais JE, Rijnhart-de Jong H, Gooszen HG (2003) Impact of anatomical wrap position on the outcome of Nissen fundoplication. *Br J Surg* 90:854–9
15. Chen Z, Zhao H, Sun X, Wang Z (2018) Laparoscopic repair of large hiatal hernias: clinical outcomes of 10 years. *ANZ J Surg* 88:E703–E707

16. Zahiri HR, Weltz AS, Sibia US, Paranj N, Leydorf SD, Fantry GT, Park AE (2017) Primary versus redo paraesophageal hiatal hernia repair: a comparative analysis of operative and quality of life outcomes. *Surg Endosc* 31:5166–5174
17. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A (2015) Global cancer statistics, 2012. *CA Cancer J Clin* 65:87–108
18. IKNL Nederlandse Kankerregistratie (NKR). <https://www.cijfersoverkanker.nl>. Accessed 20 Nov 2018
19. Van Hagen P, Hulshof MCCM, Van Lanschot JJB, Steyerberg EW, Henegouwen MI van B, Wijnhoven BPL, Richel DJ, Nieuwenhuijzen GAP, Hospers GAP, Bonenkamp JJ, Cuesta MA, Blaisse RJB, Busch ORC, ten Kate FJW, Creemers G-J, Punt CJA, Plukker JTM, Verheul HMW, Bilgen EJS, van Dekken H, van der Slangen MJC, Rozema T, Biermann K, Beukema JC, Piet AHM, van Rij CM, Reinders JG, Tilanus HW, van der Gaast A (2012) Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer. *N Engl J Med* 366:2074–2084
20. Shapiro J, van Lanschot JJB, Hulshof MCCM, van Hagen P, van Berge Henegouwen MI, Wijnhoven BPL, van Laarhoven HWM, Nieuwenhuijzen GAP, Hospers GAP, Bonenkamp JJ, Cuesta MA, Blaisse RJB, Busch ORC, ten Kate FJW, Creemers GJM, Punt CJA, Plukker JTM, Verheul HMW, Bilgen EJS, van Dekken H, van der Slangen MJC, Rozema T, Biermann K, Beukema JC, Piet AHM, van Rij CM, Reinders JG, Tilanus HW, Steyerberg EW, van der Gaast A (2015) Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): Long-term results of a randomised controlled trial. *Lancet Oncol* 16:1090–1098

APPENDIX II

List of publications



JOURNAL ARTICLES

Jezerskyte E, Mertens AC, Dieren S van, Eshuis WJ, Sprangers MAG,

Van Berge Henegouwen MI, Gisbertz SS (2022)

Gastrectomy Versus Esophagectomy for Gastroesophageal Junction Tumors.

Ann Surg 276:e735–e743. <https://doi.org/10.1097/SLA.0000000000004610>

Van Mens HJT, Martens SSM, Paiman EHM, Mertens AC, Nienhuis R, de Keizer NF, Cornet R (2022)

Diagnosis clarification by generalization to patient-friendly terms and definitions: Validation study.

J Biomed Inform 129. <https://doi.org/10.1016/J.JBI.2022.104071>

Mertens AC, Gooszen J, Fockens P, Voermans R, Gisbertz S, Bredenoord A,

Van Berge Henegouwen MI (2021)

Treating Early Delayed Gastric Tube Emptying after Esophagectomy with Pneumatic Pyloric Dilation.

Dig Surg 38:336–341. <https://doi.org/10.1159/000519785>

Mertens AC, Kalff MC, Eshuis WJ, Van Gulik TM, Van Berge Henegouwen MI, Gisbertz SS (2021)

Transthoracic Versus Transhiatal Esophagectomy for Esophageal Cancer: A Nationwide Propensity Score-Matched Cohort Analysis.

Ann Surg Oncol 28:175–183. <https://doi.org/10.1245/S10434-020-08760-8>

Gertsen EC, de Jongh C, Brenkman HJF, Mertens AC, Broeders IAMJ, Los M, Boerma D, ten Bokkel Huinink D, van Leeuwen L, Wessels FJ, van Hillegersberg R, Ruurda JP (2020)

The additive value of restaging-CT during neoadjuvant chemotherapy for gastric cancer.

Eur J Surg Oncol 46:1247–1253. <https://doi.org/10.1016/J.EJSO.2020.04.002>

Mertens AC, Tolboom RC, Zavrtanik H, Draaisma WA, Broeders IAMJ (2019)

Morbidity and mortality in complex robot-assisted hiatal hernia surgery: 7-year experience in a high-volume center.

Surg Endosc 33:2152–2161. <https://doi.org/10.1007/s00464-018-6494-4>

Van't Hullenaar CDP, Mertens AC, Ruurda JP, Broeders IAMJ (2018)

Validation of ergonomic instructions in robot-assisted surgery simulator training.

Surg Endosc 32:2533–2540. <https://doi.org/10.1007/S00464-017-5959-1>

BOOK CHAPTERS

Mertens AC, Broeders IAMJ (2021)

Redo Hiatal Hernia Surgery: Robotic Laparoscopic Approach.

Robot Surg 659–664. https://doi.org/10.1007/978-3-030-53594-0_51

Mertens AC, Broeders IAMJ (2019)

Adverse Events in Robotic Assisted Hiatal Hernia Repair.

Robot Assist Hernia Repair 489–499. https://doi.org/10.1007/978-3-030-23025-8_32

APPENDIX III

Acknowledgements



DANKWOORD

Na meer jaren dan ik voor mijzelf wil toegeven is het dan eindelijk af. Ik ben ongelooflijk trots op het werk dat in dit boekje beschreven staat, maar ik heb het natuurlijk niet alleen gedaan. Een aantal personen wil ik in het bijzonder bedanken.

Geachte prof. Broeders, beste Ivo, over de afgelopen jaren heb ik je leren kennen als een van de toonaangevende chirurgen binnen je vakgebied, onderzoeker met een uitstekend oog voor detail en een feilloos kompas voor ethiek en het vermijden van onzin. Van jou heb ik mogen leren wanneer zowel onderzoek als een medische behandeling leuk klinkt maar uiteindelijk geen meerwaarde heeft, en wanneer het de moeite waard is om er voor te gaan. Als ANIOS op de afdeling chirurgie en later op de refluxpoli heb ik ontzettend veel van je geleerd over het medisch vakgebied, maar ook over hoe je nou echt voor een patiënt kan zorgen. De betrokkenheid die jij toont zal me altijd bijblijven als een voorbeeld. Bedankt professor!

Geachte dr. Draaisma, beste Werner. Er zijn maar weinig mensen die je tijdens een dienst midden in de nacht kan bellen om een complexe casus voor te leggen waarvan je zonder pauze direct een doordacht antwoord krijgt. Je scherpe analytische blik heeft diepe indruk op me gemaakt, zowel in de kliniek als in het onderzoek. Naast deze professionele kwaliteiten zullen onze gesprekken over bijvoorbeeld de lastige beslissingen als eindverantwoordelijke in een baan als chirurg en wat er nou belangrijk is in het leven me altijd bij blijven. Hoewel onderzoek wel eens anderszins in onze drukke schema's, heb ik altijd het gevoel gehad dat je 100% achter me stond. Ontzettend bedankt voor je steun (en de zweep) tijdens dit lange proces!

Geachte prof. Van Berge Henegouwen, beste Mark, toen wij elkaar de eerste keer spraken kwam je al direct met een stortvloed aan ideeën voor projecten, en die stroom van inspiratie is volgens mij niet te stoppen. Dat warme welkom heeft zich voortgezet in een intensieve samenwerking met als resultaat een set artikelen waar ik trots op kan zijn. Mogen participeren in de onderzoeksgroep in het AMC is iets waar ik met enorm plezier op terug kijk; een flinke groep enorm slimme koppen met een enorme drive bij elkaar, waarbij de sfeer absoluut geweldig is. Na een gesprek met jou is de weg voorwaarts altijd weer duidelijk, en lijken de obstakels niet zo groot meer. Ontzettend bedankt voor je vertrouwen, je scherpe blik op onderzoeksmethoden en begrijpelijk schrijven, het inzetten van je netwerk en je persoonlijke betrokkenheid bij mijn promotietraject!

Geachte prof. dr. Ruers, prof. dr. Geelkerken, prof. dr. Hazebroek, prof. dr. Van Hillegersberg, dr. Nieuwenhuijs en dr. Gisbertz, hartelijk dank voor de tijd en energie die u heeft willen steken in de kritische beoordeling van mijn proefschrift. Daarnaast wil ik u bedanken voor het plaatsnemen in de oppositie.

Beste Cas, dr. van 't Hullenaar. Zonder jouw vertrouwen in mijn wetenschappelijke kwaliteiten was dit hele boekwerk er niet geweest! Ons onderzoeksproject naar de ergonomie van robotchirurgie was mijn eerste kennismaking met serieus onderzoek. Het sparren over analysemethoden en navigeren door het woud van regelgeving en bureaucratie tot aan een publicatie heeft me heel veel geleerd. Ontzettend bedankt voor je vertrouwen, coaching en aanmoediging in mijn carrière in de wetenschap én op persoonlijk en chirurgisch vak! Ik ben blij dat we een jaar als collega's hebben kunnen werken, en ik vaak met jou samen aan de operatietafel heb mogen staan. De reizen naar congressen en skivakanties zal ik nooit vergeten: gelukkig hebben we de foto's nog, en anders staan je nagels nog in de Mooserwirt!

Beste Paul Wijsman, beste Paulus, jij ontzettende nuchtere wijsneus. Je bent iemand die altijd exact zal zeggen wat je denkt, en zonder uitzondering heb je dan ook nog eens gelijk. Je kennis over wetenschappelijke analyses, het leven in de achterhoek en de beste behandeling van wat voor aandoening dan ook blijft me verbazen en inspireren. De combinatie van al die kennis en een geweldige partner om mee de kroeg in te gaan is goud waard, en ik hoop dat we dat nog lang kunnen doen! Hoewel de speeltuin misschien eerder in aanmerking komt de komende tijd.. Bedankt voor alles wat je mij geleerd hebt als onderzoeker, en ik ben blij dat ik je onder al die Zweedse bussen vandaan heb kunnen houden. Als ik ooit een chirurg nodig heb weet ik je te vinden!

Beste Rob Tolboom, His parents give him little by little... Maar eigenlijk hoeft jij helemaal niets te krijgen! Jouw passie voor nieuwe projecten heeft je in de tijd dat ik je ken geleid tot ontzettend gave resultaten – of het nou om een baan bij de chirurgie gaat, een website bouwen, het domineren van de intensive care, opzetten van een nieuw functiecentrum, een PhD, AI of een opleiding tot anesthesioloog gaat, als iemand het kan ben jij het. Ik weet zeker dat ik over 30 jaar nog steeds terug denk aan de avonturen die we samen beleefd hebben. Ontzettend bedankt voor je grenzeloze inspiratie voor nieuwe projecten, nuchtere kijk op het leven, sparren over welk onderwerp dan ook en keer op keer hilarische verhalen.

Beste Pepijn van Geuns, wat was het gaaf om deel te mogen zijn van jouw onderzoeksprojecten naar grensverleggende nieuwe behandelmethoden voor middenrifbreuken! Jouw passie voor het goede leven heeft me vaak op de been gehouden wanneer de combinatie van onderzoek en werken in de kliniek de energievoorraad weer eens op een kritisch niveau gebracht had. Ik denk nog vaak terug aan de reizen naar Miami, Oostenrijk en proeverijen bij jou thuis – het wordt weer tijd!

Dr. Gisbertz, beste Suzanne, de energie en het enthousiasme dat jij uitstraalt voor klinisch werk en onderzoek is een inspiratie! Ik heb enorm veel plezier gehad aan onze samenwerking en ieder gesprek heeft me nieuwe energie gegeven. Jouw scherpe kijk op onderzoeksmethoden heeft mij heel veel geleerd, en de motiverende woorden hebben me steeds weer de energie gegeven om door te zetten wanneer het even lastig werd. Enorm bedankt voor de aanmoediging en gezelligheid!

Beste Marianne, Eliza en Eglè, wat was het leuk om met jullie samen te kunnen werken in het AMC! Jullie gezelligheid en kennis, maar ook het hebben van een uitlaatklep voor frustraties hebben mijn jaar in het AMC tot misschien wel het beste jaar van mijn onderzoekstijd gemaakt. Bedankt dat jullie me als verse binnenkomer opgenomen hebben in de groep, wat een fijne tijd, helaas is hij voorbij gevlogen!

Beste Femke, Hendrieke, Thijs, ook al waren we onderdeel van verschillende onderzoeksgroepen in het Meander, toch hebben we samen een hoop meegemaakt! Ik heb met jullie in de kliniek mogen werken, congressen bezocht, op de lange latten gestaan en veel van jullie mogen leren. Ontzettend bedankt voor de steun tijdens dit lange project!

Beste stafleden, fellows, assistenten, verpleegkundigen alle andere collega's van het Meander Medisch Centrum. Op veel manieren ben ik met jullie opgegroeid. Van een naïeve jonge student-onderzoeker en later arts, tot een jonge arts die weet hoe te handelen wanneer het reanimatiesein af gaat of een patiënt onderuit gaat op de SEH. Wat was het een gave tijd om met jullie samen te mogen werken en van jullie te mogen leren. Wat er ook op ons af kwam, met het team trokken we het altijd recht en gingen we moe maar voldaan naar huis. Ik kan me moeilijk voorstellen dat ik nog eens deel mag zijn van zo'n hecht team – bedankt voor alles!

Lieve Wietske, als een van de weinige mensen in mijn leven die dit hele proces van begin af aan heeft meegemaakt weet jij als geen ander welke offers ik heb moeten brengen om hier te komen. Naast mijn eigen koppigheid ben jij een van de grote redenen dat het af gekomen is. Ontzettend bedankt voor je aanmoediging, nuchtere analyse en uitstekende skills als klankbord.

Beste Thomas, Wouter, Sjoerd, Wendy en Rhea, wat is het fijn om zo'n vriendengroep te hebben waar je altijd het gevoel hebt dat je elkaar vorige week nog gesproken hebt – ook als ik keer op keer af moest zeggen en er dus maanden tussen zaten. We hebben nog vele spelletjes- en/of klusdagen in de toekomst en ik wil jullie heel erg bedanken voor het geduld en de relativering op z'n tijd!

Lieve Oma Snel, Monique, Erik, Jasper, Jialei en Joris, ontzettend bedankt voor jullie niet-aflatende interesse in mijn onderzoek en begrip wanneer ik weer eens niet mee kon naar een familie-uitje. Ik ben ontzettend trots dat ik tegenwoordig ook officieel deel uit mag maken van jullie georganiseerde chaos. Ik zal nooit iemand zijn die van vrije tijd houdt, maar wat meer tijd in het noorden of met jullie op de boot staat zeker weten op mijn verlanglijst!

Dear Jialei, my favorite person from the best country up north! Thank you for creating the artwork for the cover of this thesis, providing me with an endless supply of silly but surprisingly meaningful quotes, memes and the knowledge that we're suffering through this together. I don't know enough ASL to sufficiently express my gratitude, but ee ee ee might convey some of it! Future doctor, *tips hat*.

Lieve opa's, oma's, jullie maken het helaas niet meer mee, maar ik weet zeker dat jullie ongelooflijk trots zijn op deze prestatie en hoe mijn leven er nu uit ziet. Bedankt voor al jullie adviezen – ik kan er nu in ieder geval weer een afstrepen: als je ergens aan begint maak je het ook af.

Lieve Thijn en Max, ik hoop dat ik niet al teveel hoeft uit te wijden over hoe blij ik ben met onze band – dus dat doe ik dan ook maar niet. *Unskippable monologue*: ik hoop dat we tot het einde van onze dagen samen de beste restaurants mogen bezoeken en elk klein detail bekritisieren als de rasechte culinaire experts die we zijn. Ik hoop dat we tot we van onze stoel vallen samen digitale draken een kopje kleiner mogen maken of een ruimtereis laten eindigen in een onbedoelde explosie van ons eigen schip. Ik hoop dat we nog heel vaak samen (inclusief Max) zullen roepen 'NIET MET VUUR MAX', vlak voordat iedere mogelijke positieve uitkomst van de situatie in rook op gaat. Jullie zijn een stel debielen, ik hou ontzettend veel van jullie en ben trots op wie jullie zijn geworden.

Lieve Annemiek en Lynn, wat zijn jullie perfecte partners voor jullie respectievelijke ongeleide projectielen. Ik ben blij dat jullie bij de familie horen, en hoop dat we elkaar uit blijven lachen onder het genot van een gin-tin.

Lieve pap en mam, toen ik hier mee begon zag ik naast enige trots ook de angst in jullie ogen voor wat er zou komen. Jullie onvoorwaardelijke steun en de moeite die jullie doen om mij geen richting op te leggen heeft mij de ruimte gegeven om mijn eigen pad te vinden met een warm nest om op terug te vallen. Ook al is het vanaf het allereerste begin altijd 'Sander zelf doen' geweest: zonder die vrijheid was ik hier nooit gekomen, en zonder jullie steun was ik ongetwijfeld al omgevallen. Ik hoop nog veel met jullie te mogen beleven en nog heel lang eindeloze discussies voor het haardvuur of op de boot te mogen voeren met een goede borrel als afsluiting.

Lieve Caitlin, ik weet niet hoe je het tot nu toe vol gehouden hebt om met deze ambitieuze afgeleide onderzoeker een leven op te bouwen waar we trots op zijn. In de tijd dat we elkaar kennen heb ik het studentenleven ingewisseld voor nachtelijke onderzoeksuurtjes in het ziekenhuis, ben ik arts geworden, hebben we elkaar tijden nauwelijks gezien door alle avond-, nacht- en weekenddiensten gecombineerd met een PhD, heb ik een carrièreswitch gemaakt naar een baan met zo mogelijk een nog hogere werkdruk, en het enige wat jij van zo'n debiele reis zegt is 'als het maar goed met je gaat'. Ondanks dat alles hebben we samen in een piepkleine studio gewoond, onze eerste flat gehuurd, een grotemensenhuis gekocht, zijn we getrouwd, en terwijl ik dit schrijf werk jij ontzettend hard aan ons volgende avontuur. Ik kan je niet genoeg bedanken voor je onvoorwaardelijke steun, de emotie en plezier die je in mijn nuchtere kijk op het leven injecteert, en het vertrouwen in ons. Lieve Caitlin, ik hou van je en kan niet wachten op de rest van ons leven!

APPENDIX IV

Curriculum Vitae Auctoris





CURRICULUM VITAE AUCTORIS

Alexander Mertens was born in The Netherlands, on January 10th 1989. Most of his youth was spent in Enschede, where he attended the Kottenpark Lyceum. During the last few years at this high school, he spent most of his time as a regatta sailor – chasing after the best performance on the water. This culminated in a Dutch championship title and a 33rd place at the World Championships in the 29er class.

Even though sailing took up most of his time, he graduated high school in 2008, after which he spent a year studying Biomedical Sciences in Utrecht. In 2009, he enrolled in medical school at the University of Utrecht. During this program, he took elective courses in radiology, anaesthesiology and surgery. These courses sparked an interest in surgery that would define the next years. He spent his research course and final internships at the Meander Medical Center.

After graduating medical school in 2016, he was accepted for a PhD program at the University of Twente in the Upper GI research group lead by prof. Broeders at the Meander Medical Center. Soon after, he started working as a surgical resident not in training at the same hospital. There he learned the true meaning of being a physician, with responsibilities in the emergency department, surgical wards and operating rooms. Later, he received a scholarship from the University of Twente which allowed him to perform the more involved experimental studies from this thesis. During this time he also spent time working at the Reflux Expert Center of the Meander Medical Center alongside prof. Broeders, giving him a detailed clinical insight into the pathology described in part one of this thesis.

When not working at the outpatient clinic he performed several studies on esophageal and gastric malignancies at the Amsterdam Medical Center. Working in this busy research center, he developed a passion for data analysis and FAIR (*findable, accessible, interoperable and reusable*) clinical data.

From 2019 to 2021, he was employed as a medical terminologist at the Dutch centre of expertise for standardisation of healthcare information and eHealth, Nictiz. Here, he focussed on the practical implications of standardizing medical data and how this data can be leveraged to improve healthcare.

After his time at Nictiz he started a new adventure at Meditools, a company creating a new generation of electronic health records for general practitioners. Here, he is currently employed as the Chief Information Officer, where he combines his knowledge of the clinical practice, medical terminology, software development and data analysis. Sander lives in Zeist with his wife Caitlin.

