DON'T MIND THE GAP

Esophageal replacement strategies and
future perspectives for long-gap esophageal atresia

Gabriele Gallo

586319-L-bw-Gallo
Processed on: 28-11-2022

Printed by Ipskamp Printing
Enschede, the Netherlands

Design & layout Bianca Pijl, www.pijlldesign.nl
Groningen, the Netherlands

586319-L-bw-Gallo
Processed on: 28-11-2022

DON'T MIND THE GAP

Esophageal replacement strategies and future perspectives for long-gap esophageal atresia

Oesofagus vervangende strategieën en toekomstige perspectieven voor long-gap oesofagus atresie
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof.dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

donderdag 26 januari 2023 des middags te 2.15 uur

door

Gabriele Gallo

geboren op 11 april 1986
te Avellino, Italië

Promotoren
Prof. dr. M.Y.A. Lindeboom
Prof. dr. J.B.F. Hulscher

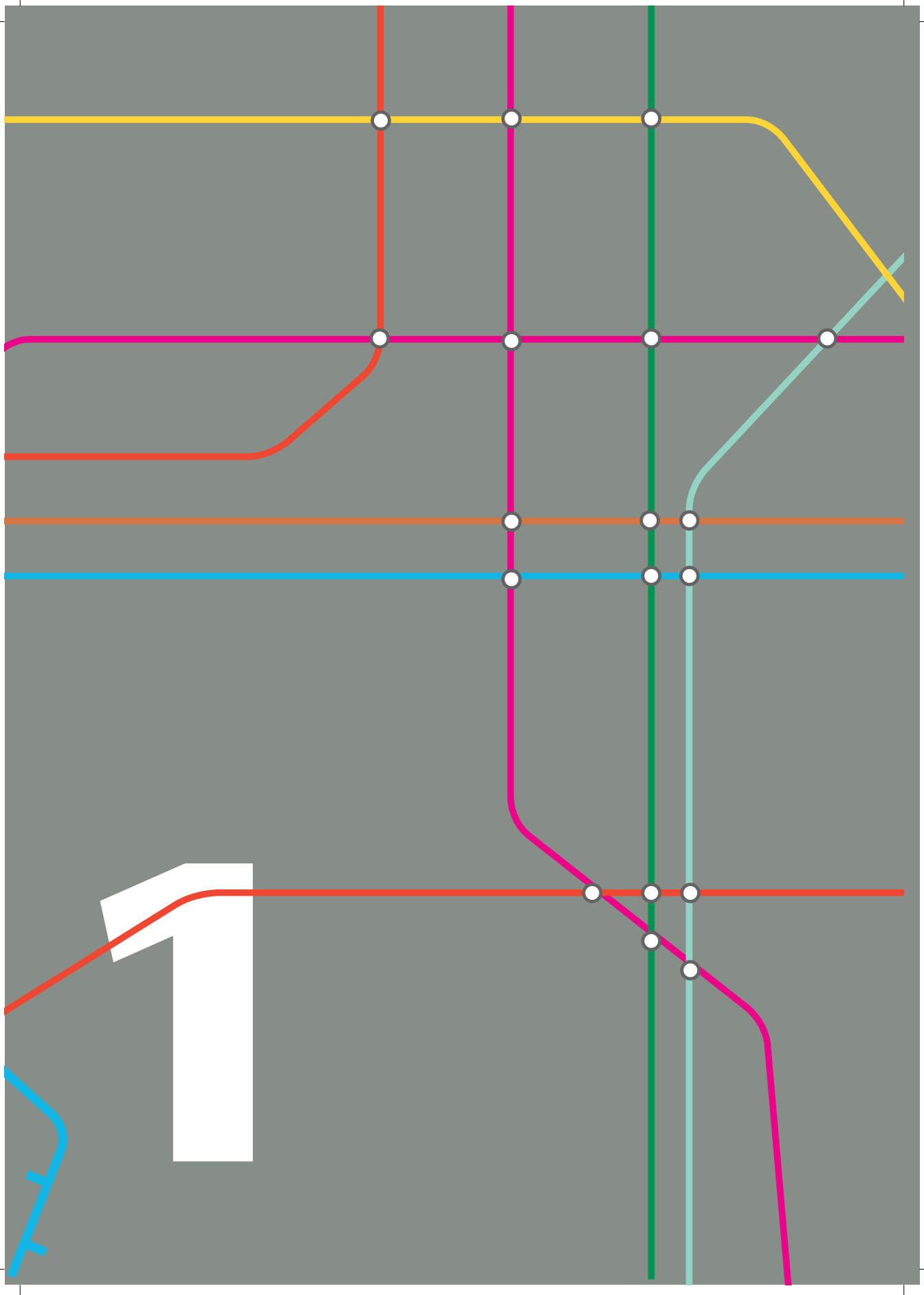
Copromotoren
Dr. S.H.A.J. Tytgat
Dr. S. Zwaveling

Beoordelingscommissie
Prof. dr. M.N. Bekker (voorzitter)
Prof. dr. E.M. van de Putte
Prof. dr. M.C.W. Spaander
Prof. dr. C.M. Bilardo
Dr. S.W.J. Terheggen - Lagro

Paranimfen
Fabrizio Bianchi
Francesco Mecozzi

TABLE OF CONTENTS

Chapter 1	General introduction	9
Chapter 2	Long-Gap Esophageal Atresia: a Meta-Analysis of Jejunal Interposition, Colon Interposition, and Gastric Pull-Up	23
Chapter 3	A two-center comparative study of gastric pull-up and jejunal interposition for long-gap esophageal atresia	37
Chapter 4	Respiratory function after esophageal replacement in children	53
Chapter 5	Graft dilatation and Barrett's esophagus in adults after esophageal replacement in long-gap esophageal atresia	73
Chapter 6	Quality of life after esophageal replacement in children	91
Chapter 7	Thoracoscopic traction technique in long-gap esophageal atresia: entering a new era	113
Chapter 8	Summary and general discussion	129
Chapter 9	Dutch summary – Nederlandse samenvatting	139
Appendices		149
	List of publications	151
	About the author	153
	Dankwoord	155


1

CHAPTER 1

General introduction

ESOPHAGEAL ATRESIA (EA)

Esophageal atresia (EA) is a congenital malformation of the esophagus with a prevalence of 2.5 to 3 per 10.000 births in Europe[1].
The most common type (85%) is Gross type C (figure1), with a distal tracheoesophageal fistula (TEF)[2].
In almost 50% of the patients, EA is accompanied by one or multiple associated anomalies, often as part of the VACTERL spectrum which includes vertebral, anorectal, cardiac, tracheoesophageal, renal, or limb anomalies[3].

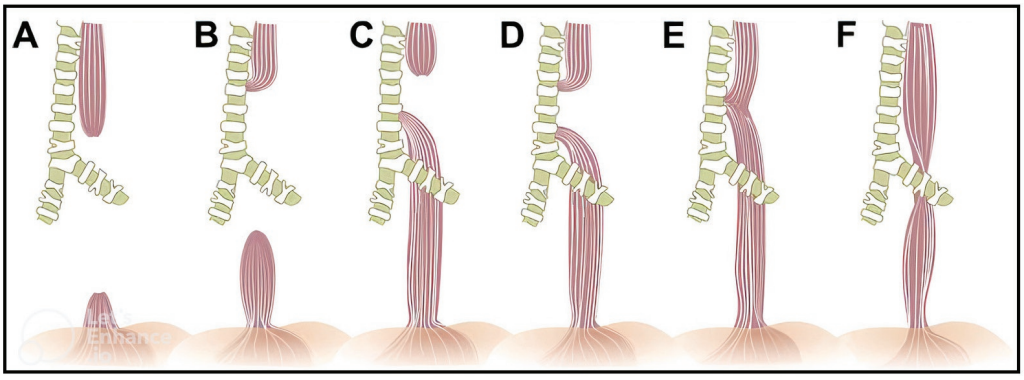


Figure1 | Gross classification of EA

EA requires surgical correction to restore the continuity of the esophagus. With improved neonatal care, the current focus in outcome has shifted from mortality to morbidity[4].
Long term sequelae occur frequently and require lifelong management and follow-up.

PRENATAL DIAGNOSIS

Suspicion of EA is based on a polyhydramnios, a small or absent stomach bubble or a blind-ending dilated upper esophageal pouch ("pouch sign") on prenatal ultrasound[5]. When EA is suspected, prenatal counseling is performed and, in the Netherlands, delivery will preferably occur in one of the three Dutch centers of expertise (CoE).

Preoperative phase

Clinical symptoms in newborns with EA usually include blowing bubbles, inability to swallow saliva or drink feeds and respiratory distress. The most common sign of EA is the inability to advance a nasogastric tube during postnatal care. A subsequent abdominal/chest X-ray will confirm a curled nasogastric tube in the proximal esophageal pouch. When EA is suspected, the nasogastric tube is replaced by a Replogle® tube for suction in the proximal pouch to prevent aspiration of saliva. All EA patients are screened for further possible VACTERL associated anomalies. In the absence of major heart anomalies, surgical repair is planned preferably within a few days after

birth and consists of a primary anastomosis of the esophagus (esophago-esophagostomy) with ligation of the TEF. Surgical repair can be performed via minimal invasive surgery (thoracoscopy) or thoracotomy[5].

In the Netherlands diagnosis, informed consent and surgical correction must be performed in a CoE. In order to improve the quality of care of EA patients designated CoE have been appointed by the Dutch government. These centers have extensive experience in pre-, peri-, and postoperative care of patients with all types of EA including long-gap esophageal atresia. CoE's offer prenatal diagnosis and counseling facilities and have highly specialized departments of neonatology and anesthesiology. All kinds of concomitant associated anomalies can be managed in CoE as well as all post-operative complications and long-term sequalae. Moreover, CoE's offer a structured, multidisciplinary follow-up program and transition to adult care[6].

LONG-GAP ESOPHAGEAL ATRESIA (LGEA)

LGEA is a rare type of EA and occurs in approximately 10% of EA patients. Recently, a working group of the International Network of Esophageal Atresia (INoEA) defined LGEA as "any type of EA in which there is no abdominal air on plain abdominal radiography, which implies EA Gross type A or B". It is important to realize that this defines EA without a distal TEF [2].

The distance between the two esophageal remnants in LGEA is too wide to perform a primary anastomosis, therefore esophageal replacement (ER) strategies can be used. Replacement with stomach, jejunum or colon have all been advocated. More recently, a thoracoscopic external traction technique (TTT) followed by esophago-esophagostomy has been developed to bridge the long-gap. TTT might form a promising strategy for LGEA patients. However, it is a novel procedure that is performed only in selected highly-expertise centers. Therefore, limited data have been published.

SURGICAL CORRECTION

Gastric Pull-Up

The most frequently performed type of ER is the gastric pull-up (GPU). This technique is regarded as the least complicated ER procedure.

After a transverse laparotomy the greater curvature of the stomach is mobilized by ligating and dividing the vessels in the gastrocolic omentum and the short gastric vessels. The vessels should be ligated well away from the stomach wall in order to preserve the vascular arcades of the right gastroepiploic vessels. The lesser curvature of the stomach is freed by dividing lesser omentum from the pylorus to the diaphragmatic hiatus, The right gastric artery is carefully identified and preserved while the left gastric artery is ligated and divided close to the stomach. The distal esophagus is dissected out of the posterior mediastinum through the diaphragmatic hiatus. The esophagus is transected at the gastrooesophageal junction and the defect closed. A pyloromyotomy is performed and the duodenum is Kocherized to obtain maximum mobility

of the pylorus. The highest part of the fundus of the stomach is identified and stay-sutures are inserted to the left and the right of the area selected for the anastomosis. These sutures help to avoid torsion of the stomach as it is pulled-up through the posterior mediastinum into the neck. The cervical esophagus is then mobilized through a neck incision. A transhiatal posterior mediastinal tunnel is created and the stomach is transposed into the neck through the esophageal hiatus and finally the esophagogastric anastomosis is performed at the apex of the stomach. The distal esophagus is resected because it is generally small and hypoplastic and preserving it would lead to anastomotic strictures[7].

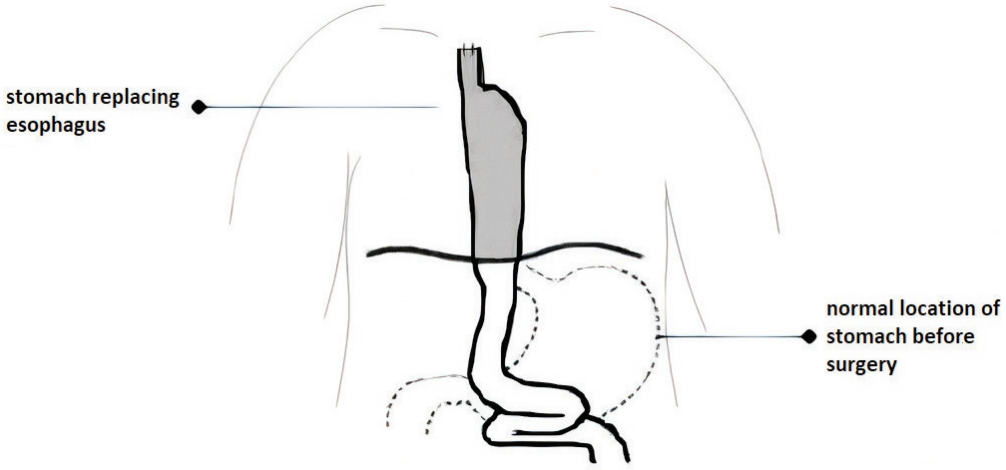


Figure 2 | Gastric pull-up technique

The main advantages of the GPU are an excellent blood supply and only one anastomosis. Graft necrosis and anastomotic complications are uncommon. However, reflux is by definition, present in the native esophagus and concerns have arisen regarding the development of Barrett's esophagus and pulmonary deterioration in the long term. Moreover, the volume of the GPU-graft in the chest may have a negative effect on respiratory function[8].

Jejunal Interposition

Another type of ER is posed by the jejunal interposition (JI).

After a median laparotomy the fundus of the stomach is detached from the diaphragm, and the upper short gastric vessels are severed. The left crus is mobilized and the posterior hiatus is opened. Access is gained behind the distal esophageal pouch into the right pleural cavity. The tunnel from the abdomen into the right chest is dilated with Hegars. Then the pedicle graft is created: the jejunum is transected close to Treitz ligament, leaving enough proximal jejunal length for restoration of continuity. The first two mesenteric artery branches are centrally divided between ligatures, leaving the peripheral arcades intact. The jejunum is transected again at the level of the third mesenteric artery branch. The distal part of the upper jejunum is skeletonized close to the bowel wall. The jejunum thus isolated is far too long. No more than the 5 proximal centimeters are needed. The distal part of the upper jejunum (b) is therefore removed, leaving the uppermost part (a) for transfer into the chest. The uppermost part of the jejunum is transferred through the left mesocolon, behind the stomach, and through the posterior part of the hiatus into the right chest, where a double anastomosis is made between the upper and lower esophagus and the jejunal graft[9].

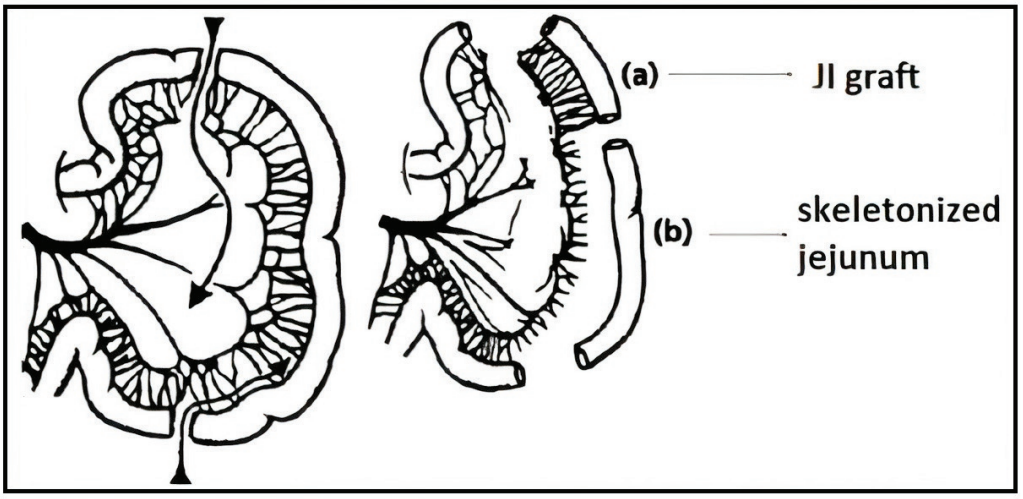


Figure 3 | Division of the mesenteric artery branches of the jejunum. *A. JI-graft with bloodsupply. B.Skeletonized distal part of the upper jejunum that will be removed.*

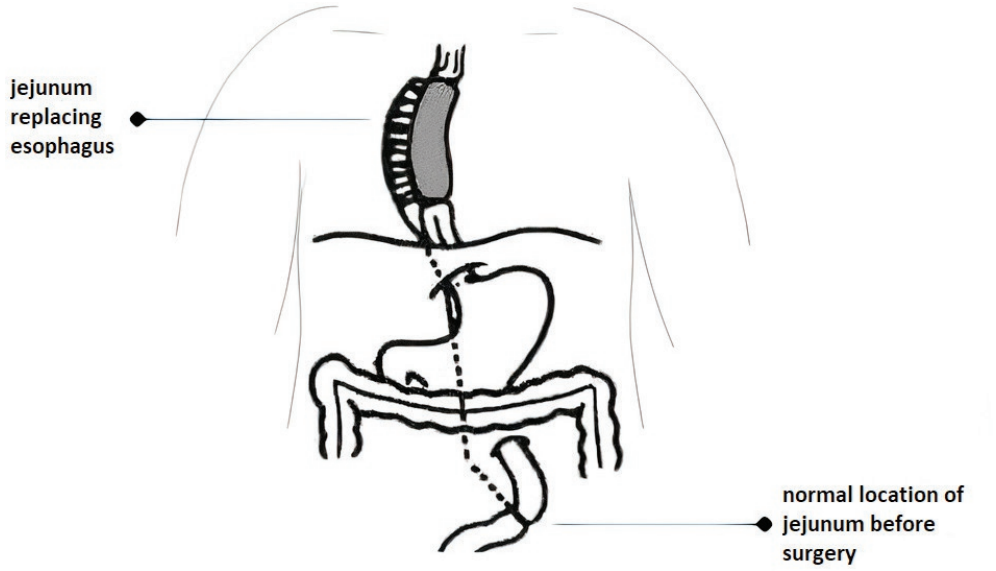


Figure 4 | Jejunal interposition technique

This JI-graft is associated with less reflux. Furthermore, the JI-graft diameter is similar to that of the esophagus. It grows at a similar rate as the child and maintains intrinsic motility. However, it is a technically challenging procedure, involving three anastomoses and a precarious blood supply of the graft. Therefore, this technique is performed only in highly experienced centers. Early postoperative anastomotic complications (eg leakage, stenosis) are more frequently reported than after GPU. Dilatation of the graft and dysphagia symptoms are also described in the long term[8].

Colon Interposition

According to the INoEA, colon interposition is mainly reserved as a last option, when all other procedures have failed or are not feasible[6].

After a median laparotomy mobilization of the colon is performed and the graft is chosen on the territory supplied by the upper left colic artery. Then the middle colic and marginal vessels are clamped by bulldogs, and the colon is left inside the abdomen to verify adequate circulation. After verification of an adequate blood supply and length the colon is resected and graft is passed behind the stomach in an isoperistaltic manner.

To facilitate passage through the chest, a silk suture is applied to the proximal end of the graft and pulled through the cervical incision until the colon is in place, either in a tunnel retrosternally or in the posterior mediastinum. Redundant parts are resected. Esophago-colic anastomosis is done, and the colon is fixated to the neck muscles. Eventually the gastro-colic anastomosis is performed at the cardia and a fundoplication is fashioned. The colon graft is finally fixed to the edge of the hiatus[10].

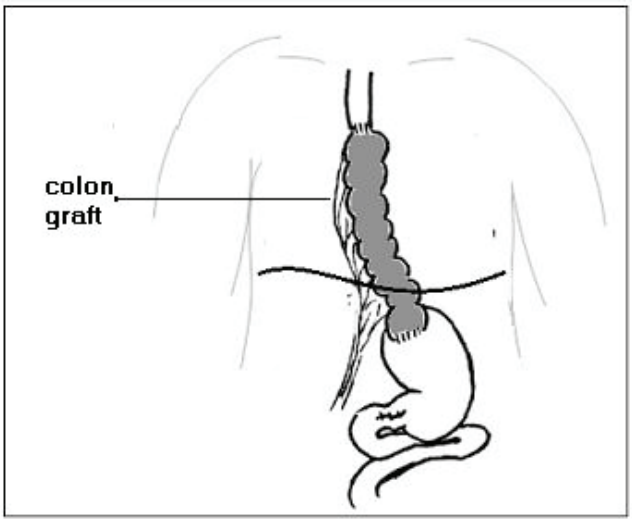


Figure 5 | Colon interposition graft

Early complications of this technique are common, such as graft necrosis due to precarious blood supply, high risk of anastomotic leakage and stricture. Long term complications include kinking due to inappropriate growth, bulging of the graft in the neck, stasis of food residue in the graft with reflux and aspiration. Advantages of this technique are represented by an adequate graft length and the fact that the graft occupies little space in chest in contrast to GPU[8].

TTT

The novel native esophagus-preserving LGEA correction is the thoracoscopic traction technique (TTT).

For the traction technique, the patient is positioned in a 3⁄4 left lateral position at the left side of the table. The proximal esophagus is mobilized to a maximal extent in the thoracic aperture. Thereafter, the distal esophagus is determined and mobilized out of the esophageal hiatus. Thoracoscopic traction sutures are placed at both esophageal ends and are fixed externally with mosquito forceps. A laparoscopic gastropexy is performed to prevent the stomach from migrating into the thorax. Approximation of the esophageal ends is evaluated by postoperative X-rays. When this approximation hampers prematurely, thoracoscopic adhesiolysis is performed. Both ends are anastomosed during a final thoracoscopic procedure. A chest tube is positioned next to the esophageal anastomosis.

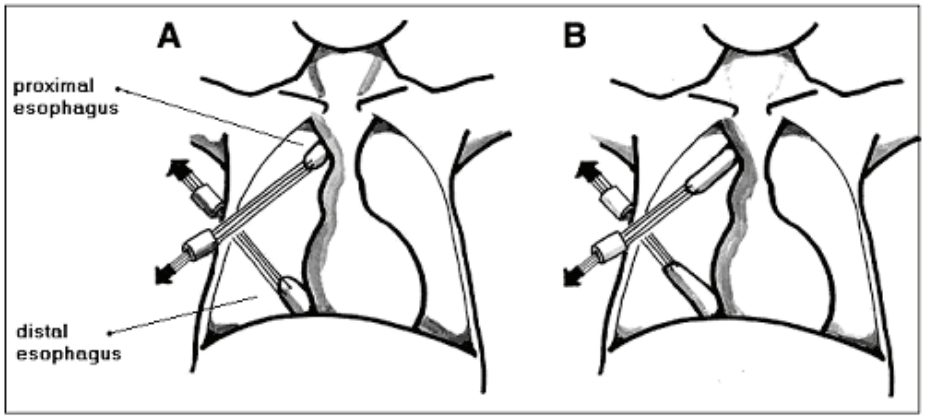


Figure 6 | Diagram of traction technique. A *Distance at start of traction.* ***B*** *Elongation of the two pouches over the days of traction.*

The major advantage of TTT is that esophageal repair can be achieved within days after birth and there is no need of a gastrostomy. Consequently, oral feeding can be started soon after birth. This may positively influence the development of adequate swallowing/feeding skills, crucial for the patients' growth[11].
Thus, there are different strategies to bridge the gap in LGEA patients. Since LGEA is a rare disease, it is difficult to develop vast expertise in the existing surgical procedures.

Current evidence on short- and long-term results originates from small-size, retrospective reports. Moreover, there is a significant heterogeneity in the chosen endpoints and well-designed comparative studies are lacking. Consequently, comparing outcome between the available studies is very challenging which makes it difficult to identify the most optimal surgical technique for LGEA.

AIMS AND OUTLINE OF THIS THESIS

This thesis focuses on Gastric Pull-Up and Jejunal Interposition, since the GPU and JI are the most frequently used ER techniques for LGEA in the Netherlands. We have deliberately chosen not to include colon interposition in this thesis, since it is considered a rescue procedure when other strategies have failed. Moreover, CI is rarely performed in the Netherlands[6].

We aimed to perform comparative studies on GPU and JI regarding short and long term data. The studies in this thesis focus on early postoperative morbidity with emphasis on anastomotic complications, long-term gastrointestinal function and reflux, respiratory morbidity, long term micro and macroscopic changes of the grafts and quality of life.

Chapter two describes a meta-analysis of the most recent studies reporting ER for LGEA. We found that literature on this topic consisted mainly of small sample size studies with broad methodological and numerical differences. For this reason, comparing the different strategies was challenging. Therefore, we chose to perform a meta-analysis in order to pool and compare data in a more objective manner. We aimed to describe an overview of early gastrointestinal and respiratory complications after surgery and morbidity during follow up.

Chapters three to six comprise several cohort studies comparing LGEA patients after GPU or JI.
In chapter three the short term and mid-term outcome of the two procedures are compared with emphasis on surgical parameters and gastrointestinal symptoms.

Chapter four focuses on the respiratory sequelae. We aimed to study if the presence of a graft in the thorax influences respiratory function. The prevalence of respiratory symptoms and lung function is investigated by using spirometry and DLCO.

Besides the effects on the respiratory system, ER can also affect the gastrointestinal system. Both changes in (patho-) fysiology and/or on a cellular level can occur. Some authors have reported an increased risk on Barrett's esophagus12 and even rare cases of esophageal carcinoma in EA patients have been reported13. In chapter five, therefore, the long-term effects on gastrointestinal function and anatomical and mucosal changes were studied in adults after GPU and JI. Assessment was performed by conducting semi-structured interviews, contrast studies and endoscopy with histopathology. We aimed to investigate whether significant changes of the native esophagus and the graft occured over time, with emphasis on reflux- and dysphagia symptoms and signs of Barrett's esophagus.

In chapter six the (health-related) quality of life (QoL) of young adults after ER for LGEA was evaluated. We aimed to answer the question whether gastrointestinal and respiratory symptoms would influence patients' well-being in daily life. To assess (HR)QoL in these patients, the GIQLI, CHF87-BREF, WHOQOL-BREF, TNO AZL TACQoL/TAAQoL were performed in 14 young adults. To date, only a few studies have investigated QoL after ER and the majority of these studies did not use validated tools[14,15].

This thesis and the first chapters focusses on the two ER procedures recommended by the INoEA for LGEA.

However, recently INoEA pointed out that all efforts should be made to preserve the patient's native esophagus and that ER techniques should be used only when primary esophageal anastomosis is not possible. Primary esophageal correction can be accomplished by delayed primary anastomosis or traction techniques. Esophageal continuity with delayed primary anastomosis is performed two to three months after birth. Besides this prolonged hospital stay, this may also lead to swallowing difficulties due to deferred introduction of oral feeding and respiratory problems mainly due to aspiration.

Thus, future strategies for LGEA could be formed by traction techniques that preserve the native esophagus. Hereafter, esophageal repair can be accomplished within days after birth.

In chapter seven we describe the results of the first cohort study reporting our experience with the TTT as a novel esophagus-preserving strategy in the treatment of LGEA. In this study we focussed on safety, feasibility and efficiency of this technique to bridge the gap.

REFERENCES

1 Sfeir R, Michaud L, Sharma D, Richard F, Gottrand F. National esophageal atresia register. Eur J Pediatr Surg 2015;25:497–9. doi: 10.1055/s-0035-1569466 .

2 Pedersen RN, Calzolari E, Husby S, Garne E; EUROCAT Working 2012;97(03):227–232

3 Epidemiology of esophageal atresia. Sfeir R, Michaud L, Salleron J, Gottrand F. Dis Esophagus. 2013 May-Jun;26(4):354-5. doi: 10.1111/dote.12051. PMID: 23679022

4 IJsselstijnH, GischlerSJ, ToussaintL, et al.Growth and development after oesophageal atresia surgery:need forlong-term multidisciplinary follow-up.PaediatrRespirRev. 2016;19:34–38

5 van der Zee DC, van Herwaarden M, Hulsker C, et al. Esophageal Atresia and Upper Airway Pathology. Clin Perinatol 44 (2017) 753–762

6 van der Zee DC, Bagolan P, Faure C, Gottrand F, Jennings R, Laberge JM, et al. Position paper of INoEA working group on long-gap esophageal atresia: for better care. Front Pediatr 2017;5:2–4. doi: 10.3389/fped.2017.0 0 063 .

7 Spitz L. Gastric transposition in children. Semin Pediatr Surg 2009;18(1):30–33

8 P. Loukogeorgakis , A. Pierro. Replacement Surgery for Esophageal Atresia. Eur J Pediatr Surg 2013; 23(03): 182-190 DOI: 10.1055/s-0033-1347915

9 Bax KM. Jejunum for bridging long-gap esophageal atresia. Semin Pediatr Surg 2009;18(1):34–39

10 Hamza AF. Colonic replacement in cases of esophageal atresia. Semin Pediatr Surg 2009;18(1):40–43

11 van der Zee DC, Gallo G, Tytgat SHA. Thoracoscopic traction technique in long-gap esophageal atresia: entering a new era. Surg Endosc 2015;29:3324–30. doi: 10.10 07/s0 0464-015-4091-3 .

12 Vergouwe FWT, IJsselstijn H, Biermann K, Erler NS, Wijnen RMH, Bruno MJ, Spaander MCW. High Prevalence of Barrett's Esophagus and Esophageal Squamous Cell Carcinoma After Repair of Esophageal Atresia. Clin Gastroenterol Hepatol 2018; 16: 513-521.e6. [DOI: 10.1016/J.CGH.2017.11.008]

13 Pultrum BB, Bijleveld CM, De Langen ZJ, Plukker JTM. Development of an adenocarcinoma of the esophagus 22 years after primary repair of a congenital atresia. J Pediatr Surg (e-pub ahead of print 2005; doi:10.1016/j.jpedsurg.2005.08.042).

14 Deurloo JA, Ekkelkamp S, Hartman EE, et al. Quality of life in adult survivors of correction of esophageal atresia. Arch Surg 2005;140:976–80.

15 S.P. Tan Tanny, et al., Quality of life assessment in esophageal atresia patients: a systematic review focusing on long-gap esophageal. J Pediatr Surgery, Available online 5 October 2019, https://doi.org/10.1016/j.jpedsurg.2019.08.040


2

CHAPTER 2

Long-Gap Esophageal Atresia: a Meta-Analysis of Jejunal Interposition, Colon Interposition, and Gastric Pull-Up

Gabriele Gallo, Sander Zwaveling, Henk Groen, David Van der Zee, Jan Hulscher

European Journal of Pediatric Surgery 2012;22:420–425.

ABSTRACT

Aim

There is still no consensus about the optimal surgical approach for esophageal replacement in the case of long-gap esophageal atresia (LGEA) or extensive corrosive strictures. The aim of this article was to perform a meta-analysis comparing the most widely used techniques for esophageal replacement in children: jejunal interposition (JI), colon interposition (CI), and gastric pull-up (GPU).

Methods

Review of the English-language literature published in the past 5 years about esophageal replacement in children was done. The focus was on postoperative survival rate, morbidity (gastrointestinal complications such as anastomotic stenosis/leakage and respiratory complications such as pneumothorax, pneumonia, and atelectasis), and long-term follow-up when available. Among long-term gastrointestinal outcomes were dysphagia, reflux, and dumping; among long-term respiratory outcomes were recurrent pneumonia and recurrent aspiration leading to chronic lung disease. Data were computed by Comprehensive Meta-Analysis software (Version 2.2.064).

Main Results

A total of 15 studies (4 comparative retrospective, 8 retrospective, and 3 prospective) including 470 patients (264 LGEA) were identified; 344 (73%) patients underwent CI, 99 (21%) GPU, and 27 (6%) JI. Among these 15 studies, 9 provided data about long-term follow-up.

Conclusion

Proper prospective comparative studies are lacking. GPU and CI appear comparable regarding postoperative mortality, anastomotic complications, and graft loss. On the long-term, GPU seems to be associated with a higher respiratory morbidity but fewer gastrointestinal complications than CI. Based on this article only two series provide data about JI, and they show highly divergent results. JI appears to be a valid replacement technique when performed by experienced centers; however larger numbers are needed to assess the outcomes of this procedure.

INTRODUCTION

There is still no consensus about the optimal surgical approach for esophageal replacement in the case of long-gap esophageal atresia (LGEA) or extensive corrosive strictures. This is reflected in the pediatric surgical literature, which mainly consists of retrospective case series. To provide an overview of the literature of the past 5 years, taking into account the methodological and numerical differences among the considered studies, we have performed a meta-analysis comparing the three most widely used techniques for esophageal replacement in children: jejunal interposition (JI), colon interposition (CI), and gastric pull-up (GPU).

METHODS

Literature

A literature search (PubMed and Embase) was performed, and all human studies published in the English-language literature between 2006 and 2011 describing esophageal replacement for LGEA were identified, using the medical subject headings "Esophageal Atresia," "Long-gap," "Esophagoplasty," "Replacement," "Interposition," "Substitution," "Graft," and their combinations. All titles and abstracts were scanned and appropriate citations were reviewed. Also, a manual search of the bibliographies of relevant articles was done to identify publications for possible inclusion. Included were prospective, retrospective, and comparative studies. Case reports, earlier reports of the series that were republished by the same center, review articles summarizing results of previous series, and the publications that did not provide sufficient data for the analyses mentioned above were excluded.

Definition of Outcomes

The articles were reviewed with a special focus on mortality, postoperative morbidity, and long-term follow-up. Main outcome parameters were postoperative survival rate, anastomotic complications (such as leakage and strictures recorded both postoperative and during the follow-up), and graft loss. Secondary outcome parameters were early respiratory complications (pneumothorax, pneumonia, atelectasis, mediastinitis, pleural effusion, and temporary diaphragm/vocal cord paresis), hospital stay, and intensive care unit (ICU) stay. Long-term follow-up was focused on gastrointestinal and respiratory outcomes, when defined. Long-term gastrointestinal outcomes were dysphagia, reflux, dumping, esophagus ulceration, anastomotic diverticulum, cervical fistula, graft redundancy, graft ulceration, intestinal obstruction, short bowel syndrome, dumping syndrome, delayed gastric emptying, cyclical vomiting, pyloric stenosis, diarrhea, colitis, peritonitis, small intestinal ischemia, and stomach perforation. Long-term respiratory outcomes were recurrent pneumonia, recurrent aspiration leading to chronic lung disease, and chest infection. Complications were recorded as stated in the article under review. When possible the exact number of specific complications were identified, otherwise the article was not included in the analysis (for that specific outcome).

Statistical Analysis

Studies were divided into the following three groups: JI, CI, and GPU. To perform the statistical overview Comprehensive Meta Analysis software (Version 2.2.064) was used. Data were computed using a random effects approach. To ensure that all effect sizes are represented in the calculated estimate, we did not perform a fixed effects analysis as we wanted to avoid giving more or less weight to larger or smaller studies. Under the random effects model the goal is not to estimate one true effect, but rather to estimate the mean of a distribution of effects in a range of studies, thus avoiding the overall estimate to be overly influenced by any study. Therefore, to obtain the most precise estimate of the overall mean (to minimize the variance among studies, given by within-study variance and the between-studies variance) we computed a weighted mean, where the weight assigned to each study is the inverse of that study's variance. Furthermore when the event rate in a study was equal to 0, 0.5 was added to event and nonevent values for the computation of Logit event rate and its variance[1].

However, there are only two studies regarding JI and the reported results differ widely. Because of this large divergence in results, calculating only an overall weighted mean using a random effects model seems inappropriate. For this reason, we present both the raw data and the weighted mean as described previously. Relative risks (RRs) were computed using JI as the standard to which the other procedures were compared. This implies that the treatment benefit for CI and GPU when compared with JI was associated with an RR less than 1.

RESULTS

Data Collection

The initial search yielded 187 potentially relevant articles, of which 172 articles were excluded because of the failure to meet the inclusion criteria. A total of 15 studies fulfilled the inclusion criteria and were analyzed in this review. (Table 1)[2-16]. Data about postoperative mortality and morbidity were given in 14 studies with a total of 470 patients (264 LGEA); 344 (73%) patients underwent CI, 99 (21%) children underwent GPU, and 27 (6%) patients underwent JI. Among these studies nine reported follow-up data. One of these studies focused exclusively on follow-up after the treatment of corrosive esophageal strictures. This study was also included in the present article (107 patients treated by GPU and 69 by CI), so that long-term gastrointestinal data were available for 394 children: 207 (52%) after CI, 27 (7%) after JI, 160 (41%) after GPU. Respiratory data were available for 377 children: 190 after CI (50%), 27 after JI (7%), and 160 after GPU (43%). The majority of long-term data regards patients treated for corrosive strictures, followed by those treated for LGEA. The follow-up period ranged from 0.5 to 41 years

Table 1 | Articles included in the present study

Author (year)	Replacement performed	Patients suitable for the present analysis	Study type
Tannuri et al (2007)	CI/GPU	115	Comparative Retrospective
Hunter et al (2009)	CI/GPU	11	Comparative Retrospective
Holland et al (2009)	CI/GPU	25	Comparative Retrospective
Javed et al (2011)	CI/GPU	176	Comparative Retrospective
Burgos et al (2009)	CI	96	Retrospective
Hamza (2009)	CI	97	Retrospective
Esteves et al (2010)	CI	5	Retrospective
Coopman et al (2008)	CI	17	Retrospective
Bax (2007)	JI	19	Retrospective
Cauchi et al (2007)	JI	8	Retrospective
Stanwell et al (2010)	GPU	5	Retrospective
Tannuri et al (2008)	GPU	35	Retrospective
Gupta et al (2007)	GPU	27	Prospective
Esteves et al (2009)	GPU	4	Prospective
Sharma et al (2011)	GPU	6	Prospective

Abbreviations: CI, colon interposition; GPU, gastric pull-up; JI, jejunal interposition.

Main Outcome Measures

Mortality is similar: postoperative survival rate after CI was 96%, after GPU 90.4%.

Anastomotic strictures (16.3% after CI vs 17.7% after GPU) and graft loss (4.2% after CI vs 4.8% after GPU) are comparable. after these two procedures. Anastomotic leaks are reported more frequently after GPU (24.1 vs 17.3% after CI). Regarding JI, neither Bax nor Cauchi et al describe postoperative deaths. Both mention the occurrence of anastomotic strictures in 50% of the patients. Cauchi et al's series stands out by the high incidence of graft loss (37% vs no graft loss in Bax's series) and a higher incidence of anastomotic leakage (50 vs 26% in Bax's series). Reoperations (because of graft loss, evisceration, and redo anastomosis because of anastomotic leaks) were necessary in 15% of patients (4/27) after JI (4/8 in Cauchi et al's series vs 0/19 in Bax's series), in 6% (21/344) after CI, and in 3% (3/99) after GPU. Early respiratory morbidity has the highest incidence after GPU (24.6%); however all the three procedures seem to be comparable for this outcome (JI 22.3%, CI 20.8%). Hospital stay and ICU stay could not be computed from the articles. Table 2a depicts the main outcome parameters, graft loss, and early respiratory morbidity.

Table 2a | Main outcome parameters by type of surgery

	Jejunum interposition				Colon interposition		Gastric pull-up	
	Weighted event rate	Events/ Total	Bax	Cauchi et al	Weighted event rate	Events/ total	Weighted event rate	Events/ total
Postoperative survival rate (%)	96.3 (77.8–99.5)	27/27	19/19	8/8	96.2 (93.3–97.9)	335/344	90.4 (82.3–95.1)	93/99
RR (95% CI)	1				0.97 (0.95–0.99)		0.93 (0.89–0.98)	
Anastomotic leakage (%)	33.9 (18.4–53.9)	9/27	5/19	4/8	17.3 (10.0–28.3)	67/344	24.1 (14.7–36.9)	21/99
RR (95% CI)	1				0.58 (0.32–1.03)		0.63 (0.33–1.22)	
Anastomotic stenosis (%)	51.9 (33.6–69.6)	14/27	10/19	4/8	16.3 (8.6–28.9)	44/344	17.7 (8.6–33.1)	16/99
RR (95% CI)	1				0.24 (0.15–0.38)		0.31 (0.17–0.55)	
Graft loss %	13.6 (0.7–77.0)	3/27	0/19	3/8	4.2 (1.5–11.0)	7/344	4.8 (1.8–12.2)	1/99
RR (95% CI)	1				0.18 (0.05–0.66)		0.09 (0.00–0.83)	
Early RS complications (%)	22.3 (10.4–41.5)	6/27	4/19	2/8	20.8 (14.8–28.3)	66/344	24.6 (12.3–3.2)	21/99
RR (95% CI)	1				0.86 (0.41–1.80)		0.95 (0.42–2.12)	

Abbreviations: CI, confidence interval; RR, relative risk.

Long-Term Gastrointestinal and Respiratory Outcomes

Tables 2b and 2c depict the long-term respiratory complications and gastrointestinal complications after the three different reconstructions. When compared with GPU, CI has more reported gastrointestinal complaints (40.3 vs 35.4%) but slightly less respiratory problems (7.0 vs 10.8%). In the JI group, the incidence of late respiratory morbidity was 38% in the Cauchi et al's series as compared with 5% in the Bax's series.

Table 2b | Long-term respiratory system complications by type of surgery

	Jejunum interposition				Colon interposition		Gastric pull-up	
	Weighted event rate	Events/ Total	Bax	Cauchi et al	Weighted event rate	Events/ total	Weighted event rate	Events/ total
Postoperative survival rate (%)	96.3 (77.8–99.5)	27/27	19/19	8/8	96.2 (93.3–97.9)	335/344	90.4 (82.3–95.1)	93/99
RR (95% CI)	1				0.97 (0.95–0.99)		0.93 (0.89–0.98)	
Anastomotic leakage (%)	33.9 (18.4–53.9)	9/27	5/19	4/8	17.3 (10.0–28.3)	67/344	24.1 (14.7–36.9)	21/99
RR (95% CI)	1				0.58 (0.32–1.03)		0.63 (0.33–1.22)	
Anastomotic stenosis (%)	51.9 (33.6–69.6)	14/27	10/19	4/8	16.3 (8.6–28.9)	44/344	17.7 (8.6–33.1)	16/99
RR (95% CI)	1				0.24 (0.15–0.38)		0.31 (0.17–0.55)	
Graft loss %	13.6 (0.7–77.0)	3/27	0/19	3/8	4.2 (1.5–11.0)	7/344	4.8 (1.8–12.2)	1/99
RR (95% CI)	1				0.18 (0.05–0.66)		0.09 (0.00–0.83)	
Early RS complications (%)	22.3 (10.4–41.5)	6/27	4/19	2/8	20.8 (14.8–28.3)	66/344	24.6 (12.3–3.2)	21/99
RR (95% CI)	1				0.86 (0.41–1.80)		0.95 (0.42–2.12)	

Abbreviations: CI, confidence interval; RR, relative risk; GIS, gastrointestinal system.

Table 2c | Long-term gastrointestinal complications by type of surgery

	Jejunum interposition				Colon interposition		Gastric pull-up	
	Weighted event rate	Events/ total	Bax	Cauchi et al	Weighted event rate	Events/ total	Weighted event rate	Events/ total
Overall late GIS complications (%)	24.0 (9.2–49.6)	6/27	3/19	3/8	40.3 (15.8–70.8)	81/207	35.4 (22.6–50.7)	54/160
RR (95% CI)	1				2.41 (1.13–5.11)		2.08 (0.96–0.46)	
Reflux	11.1 (3.6–29.4)	3/27	2/19	1/8	5.3 (0.7–30.0)	23/207	2.9 (0.3–25.1)	3/160
Dysphagia	3.7 (0.5–22.2)	0/27	0/19	0/8	7.2 (2.2–1.0.3)	16/207	7.9 (1.8–28.5)	20/160
Other	13.2 (2.6–46.4)	3/27	1/19	2/8	24.4 (8.8–51.9)	42/207	22.3 (13.0–35.5)	31/160

Abbreviations: CI, confidence interval; RR, relative risk; GIS, gastrointestinal system.

DISCUSSION

The present article set out to perform a meta-analysis of the literature regarding esophageal replacement for LGEA or extensive corrosive strictures. There are few prospective series, amounting to only 37 patients. Well-designed prospective comparative studies are lacking, major and minor postoperative complications are sometimes not properly defined, follow-up data are often deficient and when presented they are not homogenously described in the different studies. These make comparison a challenging task. Moreover, CI makes up for the majority of the surgical procedures reported. Far fewer studies describe the results of GPU and only two authors have illustrated their experience with JI.

If all studies about esophageal replacement for LGEA were similar we could compute a simple mean of the effect sizes, but considering the above mentioned methodological heterogeneity a simple comparison of the mean of the event rates described by different investigators seems inadequate. For this reason, we used a random effects model, using a weighted analysis of the most recent studies. Therefore the data depict an estimated overall effect. One should realize that this is only an approximation of reality and that conclusions should be carefully considered. However there are some tendencies that undeniably draw attention.

Importantly, there is little mortality regardless of the type of replacement. In contrast, morbidity is significant. In 470 patients, 93 early respiratory complications and 262 early gastrointestinal complications are reported. Reoperations (e.g., because of graft loss or anastomotic leaks) were necessary in 6% of patients. Reoperation was most prevalent in one of the two JI studies, mainly because of dismal results in this small series (Cauchi et al's). However, the reoperation rate of 6% probably is an underestimation, as anastomotic strictures were mentioned in 74 patients (16% of cases) and one might expect that many of these were dilated, which should be considered a reoperation. Unfortunately, only a few studies reported the number of required dilatations after anastomotic strictures, so this could not be computed in the present analysis. Although a conservative treatment of anastomotic leaks was described in the majority of the studies, redo anastomosis may have been underestimated as well in our results because a total amount of 97 anastomotic leaks was recorded. Still, in only five cases the authors clearly described a surgical revision of the leaking anastomosis. Only two series describe the outcomes after JI. Bax et al report excellent results in their relatively large series (19 patients): no graft loss, anastomotic leaks in 26% of patients, strictures in 52%, and only a few respiratory problems after a median follow-up of 5.5 years. On the contrary, Cauchi et al described a small series (eight patients) where both anastomotic strictures and stenosis were present in 50% of patients. Graft loss, a devastating complication, was reported in 38%. Furthermore in Cauchi et al's series, after a comparable follow-up of 6.4 years, chronic pulmonary disease following recurrent aspiration and chest infections occurred respectively in three and two out of eight patients. These deeply divergent findings might be related to technical issues but also the small number of patients included in the series of Cauchi et al might have influenced the results. What both studies share are the absence of postoperative death and a considerable high incidence of anastomotic complications (Table 2a). The main reason for this is the fact that the distal esophagus is usually small and hypoplastic.

End-to-end anastomosis tended to lead to a functional stenosis. Since changing the technique to a more oblique anastomosis at the distal esophagus the complication was seen less frequently. The low incidence of dysphagia might be because of the fact that jejunum retains peristaltic activity and thereby functions as an active conduit. However, this should also diminish the occurrence and severity of reflux. The data from the present meta-analysis suggest that GPU and CI are comparable regarding postoperative survival rate, anastomotic strictures, and graft loss. Anastomotic leakage might be more present after GPU. The tension sustained by the single anastomosis performed during GPU might add to this, although the incidence of anastomotic stenosis is equal to CI. Respiratory morbidity (both postoperative and long term) appears to be more prevalent after GPU. This might be related to the loss of the "Angle of His" following the mobilization of the stomach in the mediastinum. This may contribute to reflux and, as a result, to (micro) aspiration, especially when considering the negative intrathoracic pressure. Maybe most important, the bulk of the stomach is situated in the chest, which may impair respiration[17]. Long-term gastrointestinal morbidity seems to be more prevalent after CI. The gastrointestinal function after this approach might be affected by the usual absence of peristalsis in the colon, so that the transit is given only by gravity. Moreover graft redundancy was also recorded significantly more often after CI and, when leading to food retention, it could contribute to regurgitation and potentially to aspiration. A combination of these conditions might explain the higher event rate of reflux after CI when compared with that after GPU. Concluding, from this systematic review of the most recent experiences in esophageal replacement for LGEA and extensive corrosive strictures, no surgical approach emerges distinctly as the best procedure. Comparison is challenging as outcomes are reported differently. GPU and CI appear comparable regarding the main outcomes of the present study: postoperative mortality, anastomotic complications, and graft loss. GPU seems to be associated with a higher respiratory morbidity but fewer gastrointestinal complications than CI. Based on the present article only two series provide data about JI, and they show highly divergent results. JI appears to be a valid replacement technique when performed by experienced centers; however larger numbers are needed to assess the outcomes of this procedure. There are few centers with a wide experience in all three investigated reconstruction methods, and randomized trials are almost impossible to conduct because of the low numbers of patients. Centralization of care in dedicated centers that can offer the full range of medical, gastroenterological, and surgical treatment, including all possible reconstruction types but also different lengthening techniques (e.g. the Foker technique), seems paramount to further improve care for these patients. In the future, large series from these centers may offer a better insight in the results of care for this difficult patients group. In the present article the review process was complicated by the fact that the data were not homogenously described in the selected publications. To avoid this heterogeneity in the future, it might be feasible for authors to describe a structure of common outcomes to share the same setting among different reports, such as the use of standardized definitions of complications and long-term outcomes (Table 3).

Table 3 | Possible standardized outcomes

Preoperative outcomes	**Intra- and postoperative outcomes**	**Follow-up**
Gestational age	Type of surgery (open/laparothoracoscopic)	Length of follow-up
Birth weight	Age at surgery	Growth curves at last control
Type atresia	ICU stay/intubation length	Oral/tube feeding
Gap length	Standardized morbidity rate	Standardized morbidity rate
Cervical esophagostomy	– gastrointestinal: anastomotic stenosis anastomotic leaks anastomotic reinterventions graft loss	– gastrointestinal reflux dysphagia anastomotic reinterventions
	– respiratory: pneumothorax pneumonia mediastinitis pleural effusion	– respiratory aspiration recurrent pneumonia asthma like symptoms
	Mortality	Mortality

Abbreviation: ICU, intensive care unit.

REFERENCES

1 Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Introduction to Meta-Analysis. John Wiley and Sons; 2009

2 Burgos L, Barrena S, Andrés AM, et al. Colonic interposition for esophageal replacement in children remains a good choice: 33-year median follow-up of 65 patients. J Pediatr Surg 2010; 45(2):341–345

3 Hamza AF. Colonic replacement in cases of esophageal atresia. Semin Pediatr Surg 2009;18(1):40–43

4 Esteves E, Sousa-Filho HB, Watanabe S, Silva JF, Neto EC, da Costa AL. Laparoscopically assisted esophagectomy and colon interposition for esophageal replacement in children: preliminary results of a novel technique. J Pediatr Surg 2010;45(5):1053–1060

5 Coopman S, Michaud L, Halna-Tamine M, et al. Long-term outcome of colon interposition after esophagectomy in children. J Pediatr Gastroenterol Nutr 2008;47(4):458–462

6 Tannuri U, Maksoud-Filho JG, Tannuri AC, Andrade W, Maksoud JG. Which is better for esophageal substitution in children, esophagocoloplasty or gastric transposition? A 27-year experience of a single center. J Pediatr Surg 2007;42(3):500–504

7 Hunter CJ, Petrosyan M, Connelly ME, Ford HR, Nguyen NX. Repair of long-gap esophageal atresia: gastric conduits may improve outcome-a 20-year single center experience. Pediatr Surg Int 2009

8 Holland AJ, Ron O, Pierro A, et al. Surgical outcomes of esophageal atresia without fistula for 24 years at a single institution. J Pediatr Surg 2009;44(10):1928–1932

9 Bax KM. Jejunum for bridging long-gap esophageal atresia. Semin Pediatr Surg 2009;18(1):34–39

10 Cauchi JA, Buick RG, Gornall P, Simms MH, Parikh DH. Oesophageal substitution with free and pedicled jejunum: short- and long-term outcomes. Pediatr Surg Int 2007;23(1):11–19

11 Sharma S, Gupta DK. Primary gastric pull-up in pure esophageal atresia: technique, feasibility and outcome. A prospective observational study. Pediatr Surg Int 2011;27(6):583–585

12 Gupta DK, Sharma S, Arora MK, Agarwal G, Gupta M, Grover VP. Esophageal replacement in the neonatal period in infants with esophageal atresia and tracheoesophageal fistula. J Pediatr Surg 2007;42(9):1471–1477

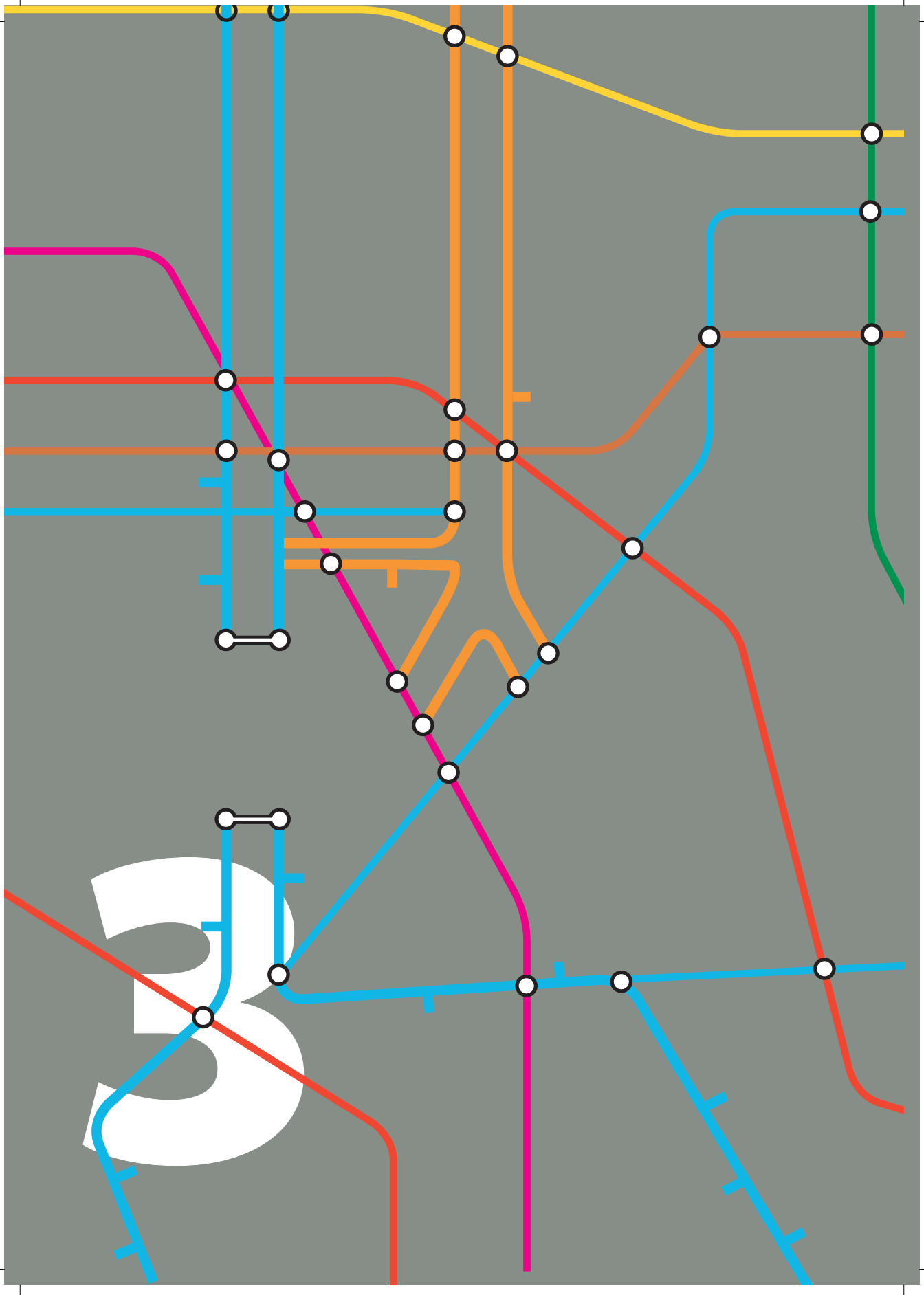
13 Tannuri U, Tannuri AC, Gonçalves ME, Cardoso SR. Total gastric transposition is better than partial gastric tube esophagoplasty for esophageal replacement in children. Dis Esophagus 2008;21(1): 73–77

14 EstevesE,SilvaMC,PaivaKC,etal.Laparoscopicgastricpull-upforlonggap esophageal atresia. J Laparoendosc Adv Surg Tech A 2009;19(Suppl 1):S191–S195

15 Stanwell J, Drake D, Pierro A, Kiely E, Curry J. Pediatric laparoscopic-assisted gastric transposition: early experience and outcomes. J Laparoendosc Adv Surg Tech A 2010;20(2):177–181

16 Javed A, Pal S, Dash NR, Sahni P, Chattopadhyay TK. Outcome following surgical management of corrosive strictures of the esophagus. Ann Surg 2011;254(1):62–66

17 Gallo G, Koppelman GH, Vrijlandt EJLE, De Langen ZJ, Hulscher JBF. Pulmonary function in children after gastric pull-up for long-gap oesophageal atresia (Abstract). EUPSA Congress; Barcelona 2011


3

CHAPTER 3

A two-center comparative study of gastric pull-up and jejunal interposition for long-gap esophageal atresia

Gabriele Gallo, Sander Zwaveling, David C. Van der Zee, Klaas N. Bax , Zacharias J. de Langen, Jan B.F. Hulscher

Journal of Pediatric Surgery 2015 Apr;50(4):535-9

ABSTRACT

Purpose

When restoration of the anatomical continuity in case of long-gap esophageal atresia (LGEA) is not feasible, esophageal replacement surgery becomes mandatory. The aim of this paper is to critically compare the experience of two tertiary referral centers in The Netherlands performing either gastric pull-up (GPU) or jejunal interposition (JI).

Methods

Retrospective chart review of all the patients with LGEA who underwent GPU in the University Medical Center Groningen and JI in the University Medical Center Utrecht. Main endpoints were short term morbidity, mortality and long-term functional outcome (digestive functioning and growth). Descriptive analyses conducted using Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables.

Results

Nine children underwent GPU and 15 JI. Median age (years) at last follow up was fourteen (GPU) and eight (JI). One patient died, 10 years after JI. No grafts were lost. Perioperative anastomotic complications were reported more often after JI (73% vs. 22%, $p = 0.03$). However, reintervention rate was the same in both groups (33%). Among long term outcomes, functional obstruction was not registered after GPU, while it was recorded in 46% after JI ($p = 0.02$). No other significant differences were found apart from some tendencies concerning full oral nutrition and gastroesophageal reflux (GPU > JI).

Conclusion

Comparative data from this study reveal no mortality but significant morbidity in both groups. No graft was lost. Although not statistically different as a result of small patient numbers, clinically important differences regarding gastrointestinal system were noted. Growth should be monitored closely in both groups.

INTRODUCTION

There is still debate on the optimal management of long-gap esophageal atresia (LGEA). When restoration of anatomical continuity is not feasible, esophageal replacement surgery becomes mandatory. To this end, replacement with jejunum[1–3], colon[4], or stomach[5] has all been advocated. However, there are little comparative data.

The aim of this paper is to report the experience of two tertiary referral centers in the Netherlands performing two different procedures for LGEA.

PATIENTS AND METHODS

A retrospective chart review of all patients who underwent gastric pull-up (GPU) for LGEA at the University Medical Centre Groningen between 1985 and 2006 was performed. Medical records of all children who underwent jejunal interposition (JI) for LGEA in the University Medical Centre Utrecht between 1988 and 2007 were reviewed for comparison. LGEA was defined as the impossibility to perform an immediate primary end-to-end anastomosis owing to the distance between the proximal and distal esophageal remnant.

SURGICAL PROCEDURES

All operations were performed by or under close supervision of one experienced pediatric surgeon in each center.

GPU

The technique as popularized by Spitz et al.[5–10] was used. In short: through a transverse laparotomy, the stomach is mobilized. The right gastric artery is preserved while the left gastric artery is divided close to the stomach. The distal esophagus is dissected. Mobilization of the duodenum is followed by a pyloromyotomy. The cervical esophagus is then mobilized through a neck incision. A transhiatal posterior mediastinal tunnel is created. The stomach is brought up into the neck through the esophageal hiatus and finally the esophagogastric anastomosis is performed at the apex of the stomach.

JI

The technique as popularized by Bax et al.[1–3] was used. In short: the diagnosis of long-gap esophageal atresia is verified by thoracot omy or in the last patient by thoracoscopy. Next a median laparotomy is performed. The fundus is detached from the diaphragm and the upper short gastric vessels are severed. The left crus is mobilized and the posterior hiatus is opened. Then the pedicle graft is created: the first mesenterial vessels are divided close to the main mesenteric route. The jejunum is transected close to Treitz ligament and severed again opposite the level of the third mesenteric branch. The jejunum is then skeletonized upwards leaving the uppermost part in place for interposition. Bowel continuity is restored and the graft with vascular pedicle is passed through the posterior hiatus into the right chest. Finally anastomoses are made between the upper and lower esophagus and the graft. All patients were admitted postoperatively to the intensive care unit and were mechanically ventilated

ENDPOINTS

Main outcome measures were perioperative morbidity and mortality, long term gastrointestinal function and growth. Most of the patients who received orthotopic jejunal pedicle graft interposition have already been described by Bax and Van der Zee[1–3]. Unlike the previous reports, the present series is a two-center study, has a longer follow up and focuses more on the long-term outcome.

Under the term *perioperative complications* all the complications reported between the day of surgery and discharge from hospital were included.

Anastomotic complications comprise both leakage and stenosis.

Anastomotic leakage was defined as extravasation of water-soluble contrast medium with or without clinical symptoms of leakage.

Anastomotic stenosis was considered as anastomotic narrowing on contrast enema with clinical symptoms of stricture/passage problems necessitating dilatation.

Pneumothorax was defined as a pneumothorax requiring a thoracic drainage.

Other thoracic complications are listed in Table 3.

In the section Long-term outcome we include mortality, gastrointestinal function, interventions and growth.

Interventions included all the reoperations after discharge from hospital, not including endoscopic procedures such as dilatation.

Under *gastrointestinal function* we report on the achievement of full oral nutrition, dysphagia, anastomotic stenosis, gastroesophageal reflux symptoms, and on the use of antacid medication and prokinetics. Symptoms of difficulty in swallowing solids without presence of reflux and graft obstruction were described under the term *dysphagia*. Graft *functional obstruction* was defined as delayed graft passage on contrast enema with associated symptoms of dysphagia but no endoscopic findings of anastomotic stenosis.

Standard deviation scores [SDSs] for height/weight were calculated using growth charts for Dutch children (corrected for Down's disease when needed), with a deviation of <–2 SD of the mean for age considered as pathological.

Statistics were computed by IBM SPSS Statistic 20 (SPSS, Chicago, IL). Descriptive analyses were conducted using Mann–Whitney U test for testing of continuous variables given a not normal distribution and Fisher's exact test for categorical variables, with a P value < 0.05 considered as significant (two-tailed test).

RESULTS

PATIENTS

Nine children underwent GPU with pyloromyotomy (eight boys, one girl) for LGEA. Orthotopic JI was performed in fifteen patients (nine boys, six girls) with LGEA.

Table 1 depicts patient characteristics. In the GPU group seven patients (77%) were prematurely born (gestational age <37 weeks); in the JI group eleven children (73%) were premature. All the GPU patients presented at least with one associated congenital anomaly, 7/15 JI children (46%) presented without any other anomaly but the LGEA. Renal malformations were seen statistically more often in the GPU group. In both groups gastrostomy was performed in every child in order to provide adequate feeding before definitive surgical correction, except in one patient who underwent GPU one day after birth. Cervical esophagostomy was performed in 4/9 GPU patients (44%) and in none of the JI patients ($p = 0.01$). No patients of the GPU group had an attempt at direct anastomosis before esophageal replacement. In the JI group 2 patients had esophageal replacement as a rescue procedure: one patient developed a long esophageal stricture after repair of an esophageal atresia with distal fistula; the second patient had two unsuccessful attempts of an open Foker technique elsewhere. There was a significant difference ($p = 0.04$) between the two groups regarding age at surgery: replacement surgery was performed earlier in the JI group (median of 63 days) than in the GPU group (median of 128 days).

One child underwent GPU at first day of life: immediate primary anastomosis in this patient was not feasible owing to an unexpected extremely short proximal esophageal segment identified perioperatively, therefore it was decided to perform directly the esophageal replacement procedure. There were no significant differences regarding hospital stay (Table 2).

Table 1 | Patients' characteristics

	GPU (n = 9)	JI (n = 15)	P value
Median gestational age (weeks)	34 (29–39)	35 (32–41)	0.36
Median birth weight (g)	1680 (1030–3040)	2220 (1115–3755)	0.57
Median age at surgery (days)	128 (1–323)	63 (23–149)	0.04
Type atresia			
No fistula	5	8	1.0
Proximal fistula	3	6	1.0
Distal fistula	1	1	0.51
Trisomy 21	0% (-)	13% (2)	0.51
Congenital anomalies			
Vertebral	55% (5)	13% (2)	0.06
Anorectal	11% (1)	13% (2)	1.00
Cardiac *	33% (3)	20% (3)	0.63
Renal **	44% (4)	6% (1)	0.04
Limbs	0% (-)	13% (2)	0.41
Duodenal atresia	11% (1)	6% (1)	1.00
Pre replacement surgery			
Gastrostomy	88% (8)	100% (15)	0.37
Cervical esophagostomy	44% (4)	0% (-)	0.01
Previous attempt at anastomosis	0% (-)	13% (2)	0.51

GPU: gastric pull-up.

JI: jejunal interposition.

*Atrial septal defect, patent ductus arteriosus, dextrocardia.

**Renal agenesis, duplex collecting system.

Table 2 | Early postoperative outcomes of 9 patients undergoing GPU and 15 patients undergoing JI for LGEA.

	GPU (n = 9)	JI (n = 15)	P value
Intensive care period	13 (3–39)	15 (4–45)	0.67
Intubation period	8 (3–36)	7.5 (1–25)*	0.92
Postoperative admission	24 (15–233)	32 (13–189)	0.18

Values expressed as days: median (range)
**Assessed in 14 patients owing to lack of data in one patient.*

PERIOPERATIVE MORTALITY AND MORBIDITY

There was no perioperative mortality and none of the grafts were lost in either group. Perioperative complications are summarized in Table 3.

Table 3 | Perioperative complications

	GPU (n = 9)	JI (n = 15)	P value
Any anastomotic complication	22% (2)	73% (11)	0.03
Anastomotic leak	22% (2)	60% (9)	0.10
Anastomotic stenosis	11% (1)	40% (6)	0.19
Pneumothorax	22% (2)	40% (6)	0.65
Other thoracic complications *	33% (3)	20% (3)	0.63
Abdominal dehiscence	11% (1)	6 % (1)	1.00
Total reintervention rate	33% (3)	33% (5)	1.00

**ARDS, capillary leak syndrome, mediastinitis, episodic aspiration pneumonia, temporary unilateral phrenic nerve paralysis.*

GPU

All nine patients (100%) reported a perioperative complication. There were two anastomotic leaks, of which one required surgery. Further surgery was necessary once for abdominal wound dehiscence and once for iatrogenic perforation of the graft during endoscopy. Stenosis was only reported once.

JI

14/15 children (93%) registered at least one complication. Patients in this group suffered statistically significant more from anastomotic complications than patients after GPU. Although statistically not significant, anastomotic leaks occurred more frequently after JI and could involve either the proximal or the distal anastomosis. The majority of these leaks could be treated conservatively, but three (33%) required surgery.

Again, although not statistically significant, there were more stenoses in the JI group. Most could be treated by dilatation but one required surgery.

One patient was reoperated for dehiscence of the laparotomy wound.

LONG TERM OUTCOME

Age

Median age at last follow-up in the GPU group was 14 years (6–19 years), in the JI group 8 years (1–19 years). Notably in the JI group one patient was only one year old at last follow-up. This could be considered as a midterm rather than a long term follow up. Median age of the patients at present is 15 years in the GPU group and 16 years for the JI group.

Mortality

There was no mortality in the GPU group at follow up. In the JI group, one patient died. This boy with trisomy 21 died at the age of 10 years in an institution most likely as a result of massive aspiration.

Long term outcome

Tables 4a and 4b describe long term functional outcomes. Functional obstruction was not registered after GPU, while it was present in 46% of the patients who underwent JI ($p = 0.02$), mainly responding to propulsitoria. No other significant differences were noted between groups regarding long term gastrointestinal and respiratory outcomes. However, a few tendencies require attention.

GPU

Three out of nine (33%) children still needed extra feeding via jejunostomy at last follow up to gain adequate daily intake. In addition, one of them required home parenteral nutrition. None of these three patients received esophagostomy at birth. Reflux symptoms were noted in 44% of the patients. Delayed gastric emptying was reported in one patient (11%).

JI

All but one (93%) patients had full oral diet at last follow up. Reflux was reported in 2 (13%) of the patients.

One patient who manifested asthma-like symptoms died at the age of ten most likely because of massive aspiration.

Table 4a | Long term digestive outcome (follow up)

	GPU (n = 9)	JI (n = 15)	P value
Patients who reported gastrointestinal problems during follow up	77% (7)	86% (13)	0.61
Full oral feeding rate	66% (6)	93% (14)	0.13
Dysphagia	11% (1)	6% (1)	1.0
Anastomotic stenosis	55% (5)	40% (6)	0.67
Median number of endoscopic dilatation per patient	3 (2–4)	4 (1–10)	
Functional obstruction	0% (-)	46% (7)	0.02
Delayed gastric emptying	11% (1)	0% (-)	0.37
Reflux symptoms	44%(4)	13% (2)	0.15
PPI's/H2-antagonists/prokinetics	66% (6)	33% (5)	0.20
Graft ulcer	0% (-)	13% (2)	0.51

Table 4b | Long term anthropometric outcomes at last follow up

	GPU (n = 9)	JI (n = 15)	P value
Height/age < −2 SD	22% (2)	30% (5)	0.66
Weight/age < −2 SD	44% (4)	26% (4)	0.41
Weight/height < −2 SD	11% (1)	20% (3)	1.00
Median BMI	15 (14–19)	15 (12–18)	0.82

INTERVENTIONS DURING FOLLOW UP

GPU

Three patients (33%) were reoperated: one for delayed gastric emptying, one for duodenal perforation during radiological placement of a feeding tube, and one for a missed proximal tracheoesophageal fistula.

JI

Three patients (19%) underwent reintervention: one patient for iatrogenic perforation of the jejunum during an endoscopic dilatation procedure, one patient for functional obstruction of the distal anastomosis despite multiple dilatations and failed widening plasty of the distal anastomosis (the distal esophagus was resected and an anastomosis made between the jejunum and the stomach; however this resulted in severe gastroesophageal reflux and pulmonary problems); and a last one patient, affected by Down syndrome, for functional short bowel syndrome, requiring feeding by ostomy.

GROWTH

Data are given in Table 4b and Figure 1.
In the GPU group an SDS below −2 for weight/age was registered in 44% of the children vs 26% in the JI group.

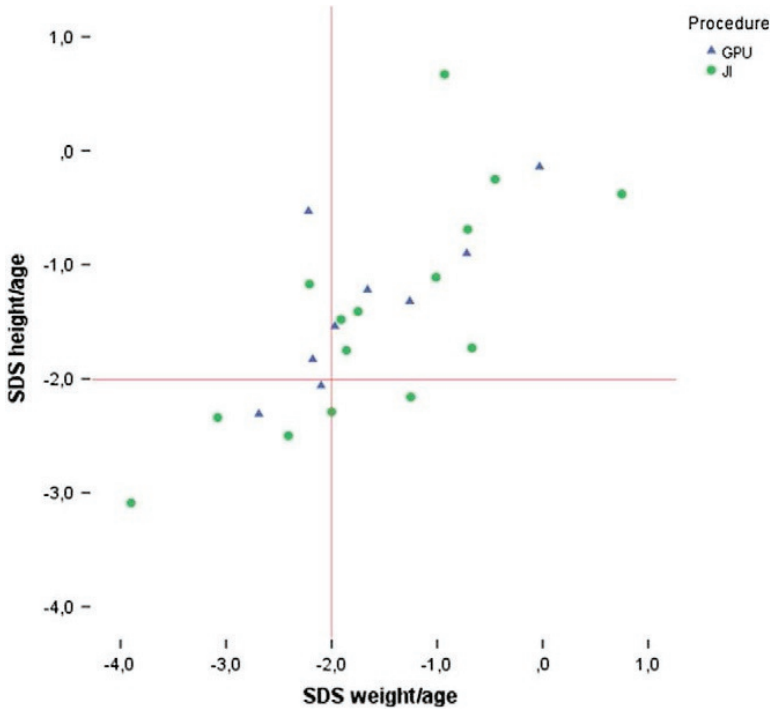


Figure 1 | Growth at last follow up

DISCUSSION

This paper is the first to systematically compare the results of GPU with JI for LGEA. There was no perioperative mortality but one patient in the JI group died at follow up. None of the grafts were lost. While the pulled up stomach has abundant blood supply, this is less generous in jejunal grafts. The stomach can therefore be brought up high into the neck without problems but this is more challenging when using jejunum. Long pedicle grafts can be constructed but such grafts have tendency to curl. Moreover, long pedicle grafts are constructed at the expense of the remaining jejunum. In the present series no thoracotomy was performed but a mediastinal tunnel was created, which is certainly less invasive than JI. Gastric pull-up using minimal access principles has been described[11,12].

JI had a significantly higher perioperative total anastomotic complication rate than GPU. When these complications were broken down into leakage and stenosis, the differences were not significant anymore but still the percentages were higher in JI. Notably, in contrast to GPU in JI two anastomoses have to be made. Leakage and stenosis rate in GPU in the present study were respectively 22% and 11%. Only one leak needed surgery. Spitz et al.[9] reported in his GPU series a comparable 12% leakage rate and a 19% stenosis rate. Only one leak required surgery, which is undoubtedly related to the fact that the esophagogastric anastomosis in GPU is made in the neck.

The 60% anastomotic leakage rate after JI in the present study is high. Three of the six leaks needed surgery. In this series of JI, anastomoses were made in the thorax. The early stenosis rate in JI in the present series was twice as high than in GPU but the late stenosis rate was similar. Two stenosis in the JI group needed surgery versus none in the GPU group. When the distal esophagus is left in place in JI, functional obstruction invariably occurs at the distal anastomosis, despite the retained peristaltic activity of jejunal grafts[2,3,13]. On contrast studies, it is obvious that the distal esophagus does not open up when the bolus arrives. Obstruction at the distal anastomosis with the esophagus can also be based on retained foregut remnants in the distal esophagus but this did not seem the case in the present series. Functional obstruction at the distal anastomosis has to be carefully watched as widening of the graft should be avoided. Once the graft becomes severely widened, resection of the distal anastomosis will lead to massive reflux as what happened in one case. The best treatment of functional obstruction is dilatation which was performed fairly regularly in JI patients.

As preventive measures, the creation of a wider oblique opening of the distal esophagus in order to shorten the gastroesophageal sphincter may cause less functional obstruction. Alternatively, the distal esophagus could be removed and a direct anastomosis between the jejunal graft and the cardia could be made. When performing this operation in two patients with long peptic stenosis not responding to therapy, both patients did not present with functional obstruction. These patients are not included in the present series.

Although not significantly different, 33% of the GPU patients were not on full oral nutrition at last follow up against only 6% in the JI group. This may be related to the significant difference in median age at replacement which is, twice as high in the GPU group. Moreover, only one patient in each group complained from dysphagia which is 11% in the GPU group versus 6% in the JI group. Spitz et al. reported significant swallowing problems in 30% after GPU postoperatively of which half persisted[9].

Motility of the transposed stomach remains controversial[14]. There is evidence of swallow-related motor activity in the stomach after GPU, although a propagated antegrade propulsive peristalsis does not seem to be present[15]. Rather than a reservoir, the transposed stomach seems to act like a conduit with an extremely irregular biphasic emptying pattern. This consists of an initial rapid clearance of the majority of the intragastric contents into the small bowel, followed by a more leisurely emptying[16]. Alteration of this fragile system might be responsible for functional passage problems. In the present series one patient (11%) seemed to suffer from severe delay in gastric emptying. Spitz et al.[9] reported severe delay in gastric emptying in 8.7% of the patients. Jejunum, even free grafts, retains peristaltic activity[17]. Peristaltic waves however do not lead to relaxation of the lower esophageal sphincter.

Although it might contribute to functional obstruction, one of the rationales for preserving the distal esophagus and its sphincteric mechanism in JI is to prevent back-flow of gastric contents. Though statistically not significant, 44% of children with GPU versus 13% of the children with JI reported higher prevalence of reflux symptoms. Gastroesophageal reflux has been reported in 20–67% of adult patients with GPU[18]. Reflux after GPU might be related to the mobilization of the stomach in the mediastinum with alteration of the shape owing to stretching and displacement of the gastroesophageal junction through an unnaturally wide hiatus and consequent loss of the angle of His. Furthermore, reflux is promoted by the negative intrathoracic pressure and the positive intraluminal pressure in the transposed stomach. It might also be induced by stasis of the gastric content owing to delayed stomach emptying despite pyloromyotomy. Persistent impaired vagal innervation after GPU might correlate with decreased total acid production and reduced parasympathetic activity with consequent delayed gastric clearance. Gastroesophageal reflux is no major problem after JI. It happened in two patients (13%), in one of them after resection of the distal esophagus for ongoing functional obstruction with dilatation of the graft. Saeki et al.[13] reported no reflux after JI in children. Even after initial resection of the distal esophagus reflux is not very prevalent.

However, gastroesophageal reflux might be present sub-clinically and it might lead potentially to (micro) aspiration with consequent respiratory deterioration. Unfortunately, not a congruous number of patients included in the present study underwent pH-metry in order to provide reliable data, so comparative data couldn't be provided here.

Growth in children with GPU or JI deserves attention. At last follow-up height and weight for age were above 0 SDS in one patient only; weight for height was above 0 SDS in five patients. These results are static and do not reflect the growth curves. For a correct interpretation of growth it is important to identify any amelioration or worsening over time on curves.

The main limitations of the present paper are the retrospective nature of the study and the small number of patients. Because of the small numbers, comparison is difficult and statistically not-significant differences may be clinically important. Another limitation is that procedures were carried out in two different centers; but this reflects the daily practice in the Netherlands, where different centers prefer different surgical procedures.

Moreover, respiratory function after esophageal replacement is important, especially in the light of GERD and repeated (micro) aspiration. However, a formal assessment of pulmonary function goes beyond the scope of the present paper.

The patients were operated in period covering respectively 19 and 21 years. This means less than one case per center per year. In 2011 Spitz wrote that the importance of three general aphorisms needs to be considered[19]:

1 There is a well-defined and clear relationship between volume (of cases), management outcome, and research output.
2 Most medical and surgical procedures have better outcome when performed in hospitals that do a lot of the procedure in question.
3 Increased hospital specialisation is associated with improved patient outcomes.

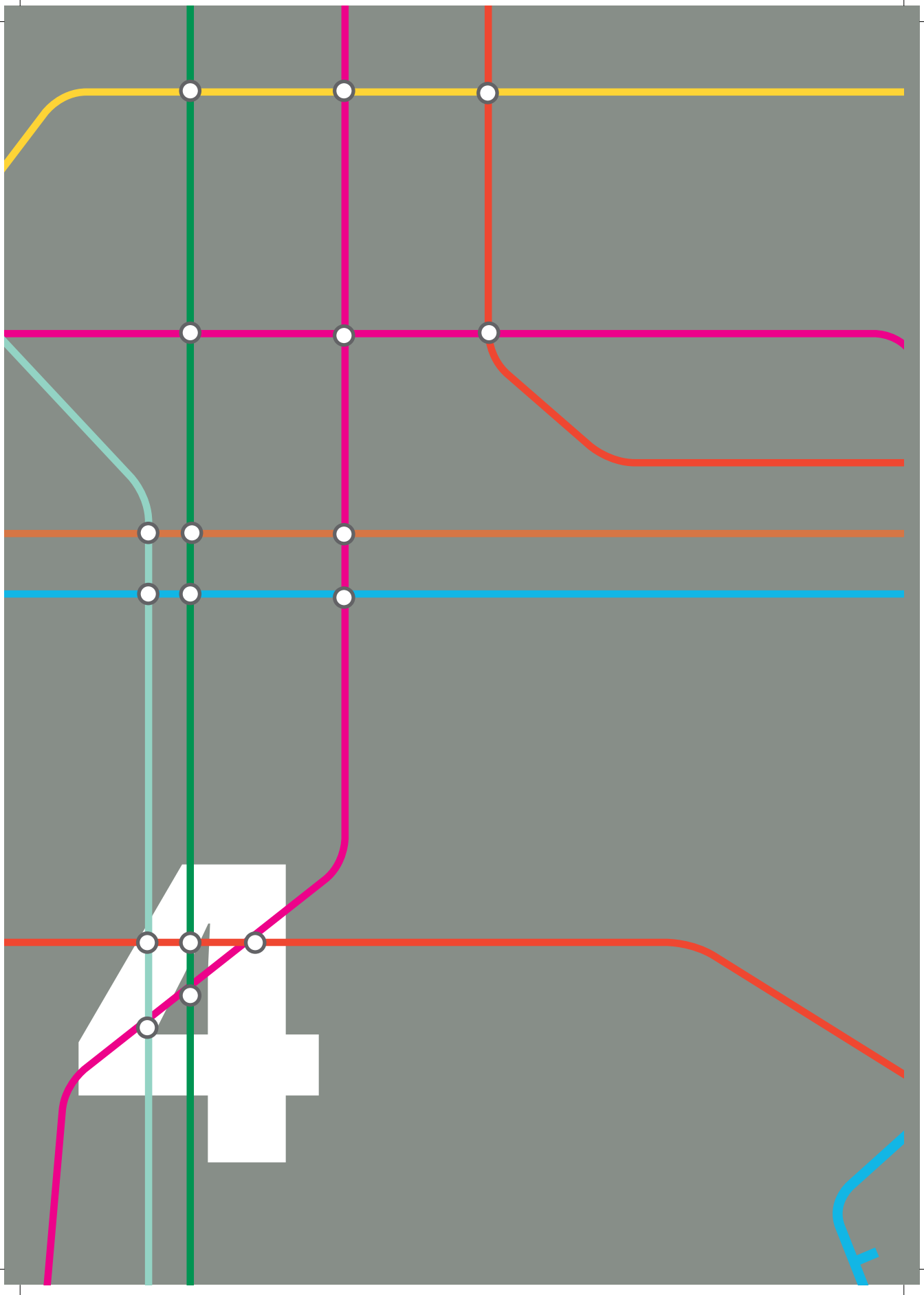
The total incidence of esophageal atresia is between 2.5 and 3 per 10,000 births[20]. Esophageal atresia without fistula accounts for about 7% of the total incidence. For the Netherlands with an actual annual birth rate of 172,000[21], 3–4 cases can be expected per year. Centralization of all these patients in one center in the Netherlands or even in a broader European context would seem appropriate. If in all cases an attempt is made at delayed primary anastomosis by using e.g. esophageal elongation technique, less cases would come to esophageal replacement making the number of children requiring an interposition even smaller.

CONCLUSIONS

GPU and JI are two optional procedures for esophageal replacement in case of LGEA. Comparative data from the present study demonstrate no mortality but significant morbidity after both procedures; patients undergoing JI suffer more frequently of early anastomotic complications and functional obstruction. There seems to be a tendency toward more reflux symptoms in the GPU group and better oral feeding ability after JI which is reflected in growth. Growth

REFERENCES

1 Bax NMA, Rövekamp MH, Pull ter Gunne AJ, et al. Early one-stage orthotopic jejunal pedicle-graft interposition in long-gap esophageal atresia. Pediatr Surg Int 1994;9:483–5.
2 Bax NMA, van der Zee DC. Jejunal pedicle grafts for reconstruction of the esophagus in children. J Pediatr Surg 2007;42(2):363–9.
3 Bax NMA. Jejunum for bridging long-gap esophageal atresia. Semin Pediatr Surg 2009;18(1):34–9. http://dx.doi.org/10.1053/j.sempedsurg.2008.10.007.
4 Hamza AF. Colonic replacement in cases of esophageal atresia. Semin Pediatr Surg 2009;18(1):40–3.
5 Spitz L. Gastric transposition for esophageal substitution in children. J Pediatr Surg 1992;27(2):252–7 [discussion 257-9. Review].
6 Spitz L. Gastric transposition via the mediastinal route for infants with long-gap esophageal atresia. J Pediatr Surg 1984;19(2):149–54.
7 Spitz L, Kiely E, Sparnon T. Gastric transposition for esophageal replacement in children. Ann Surg 1987;206(1):69–73.
8 Spitz L. Gastric transposition for oesophageal replacement. Pediatr Surg Int 1996;11(4):218–20. http://dx.doi.org/10.1007/BF00178420.
9 Spitz L, Kiely E, Pierro A. Gastric transposition in children–a 21-year experience. J Pediatr Surg 2004;39(3):276–81 [discussion 276–81].
10 Spitz L. Gastric transposition in children. Semin Pediatr Surg 2009;18(1):30–3. http://dx.doi.org/10.1053/j.sempedsurg.2008.10.006.
11 Ure BM, Jesch NK, Sümpelmann R, et al. Laparoscopically assisted gastric pull-up for long-gap esophageal atresia. J Pediatr Surg 2003;38(11):1661–2.
12 Garrett D, Anselmo D, Ford H, et al. Minimally invasive esophagectomy and gastric pull-up in children. Pediatr Surg Int 2011;27(7):737–42. http://dx.doi.org/ 10.1007/s00383-011-2862-z [Epub 2011 Feb 25].
13 Saeki M, Tsuchida Y, Ogata T, et al. Long-term results of jejunal replacement of the esophagus. J Pediatr Surg 1988;23(5):483–9.
14 Jain V, Sharma S, Kumar R, et al. Transposed intrathoracic stomach: functional evaluation. Afr J Paediatr Surg 2012;9:210–6.
15 Gupta DK, Charles AR, Srinivas M. Manometric evaluation of the intrathoracic stomach after gastric transposition in children. Pediatr Surg Int 2004;20:415–8.
16 Davenport M, Hoise GP, Tasker RC, et al. Long-term effects of gastric transposition in children: a physiological study. J Pediatr Surg 1996;31:588–93.
17 Wilson JA, Maran AG, Pryde A, et al. The function of free jejunal autografts in the pharyngooesophageal segment. J R Coll Surg Edinb 1995;40(6):363–6.
18 Yuasa N, Sasaki E, Ikeyama T, et al. Acid and duodenogastroesophageal reflux after esophagectomy with gastric tube reconstruction. Am J Gastroenterol May 2005;100(5):1021–7.
19 Spitz L. Oesophageal atresia treatment: a 21st-century perspective. J Pediatr Gastroenterol Nutr 2011;52(Suppl 1):S12.
20 Depaepe A, Dolk H, Lechat MF. The epidemiology of tracheo-oesophageal fistula and oesophageal atresia in Europe. EUROCAT Working Group. Arch Dis Child 1993;68:743–8.
21 CBS Webmagazine (Centraal Bureau voor de Statistiek - Statistics Netherlands), Monday 15 July 2013 9:30.



CHAPTER 4

Respiratory function after esophageal replacement in children

Gabriele Gallo, Elianne J.L.E. Vrijlandt, Hubertus G.M. Arets, Gerard H. Koppelman, David C. Van der Zee, Jan B.F. Hulscher, Sander Zwaveling

Journal of Pediatric Surgery 2017 Nov;52(11):1736-1741.

ABSTRACT

Background

Children born with esophageal atresia require an anastomosis between the proximal and distal esophagus. When this distance is too wide (lon-gap esophageal atresia, LGEA) esophageal replacement strategies have to be deployed. The aim of this study was to assess long-term respiratory morbidity and lung function after esophageal replacement with either stomach (gastric pull-up, GPU) or jejunum(jejunal interposition, JI) for LGEA.

Methods

Retrospective cohort study. Patients operated with GPU and JI for LGEA (1985–2007) underwent a semi-structured interview and lung function testing (LFT).

Results

Seven GPU-patients and eight JI-patients were included. Median age was 12 years. One patient per group could not perform LFT. Respiratory symptoms were reported by 13/15 patients (7/7 GPU-patients vs 6/8 JI patients). All LFT items were lower than reference values; 6/13 patients showed restriction and 6/13 obstruction. All six GPU-patients had abnormal TLC and/or FEV1/FVC vs 3/7 after JI. Restriction was noted in 4/6 GPU-patients vs 2/7 JI-patients.

Conclusion

After esophageal replacement for LGEA many children have impaired lung function and respiratory symptoms are common. Lung volumes seem decreased after GPU compared to JI. This may be caused by the intrathoracic stomach which may limit normal lung growth. Respiratory follow-up in adult life is important after esophageal replacement.

INTRODUCTION

Esophageal atresia (EA) occurs in one in 3000–5000 live births. In most patients, a direct anastomosis between the proximal and distal esophageal remnant can be constructed. When this distance is too wide (long-gap esophageal atresia, LGEA) esophageal replacement strategies have to be deployed. Replacements with jejunum[1–3], colon[4], or stomach[5] have all been advocated. Regardless of the procedure of choice, respiratory complaints are prevalent and lung function seems impaired in many patients. However, long-term data for LGEA are limited and comparative studies focusing on lung function are lacking[6–10].

Therefore, we aim to investigate the prevalence of respiratory symptoms and lung function after esophageal replacement surgery with either stomach or jejunum for LGEA in two tertiary referral centers in the Netherlands.

PATIENTS AND METHODS

A retrospective cohort study was performed. All patients who underwent gastric pull-up (GPU) at the University Medical Center Groningen (UMCG) in 1985–2006 and jejunal interposition (JI) at the University Medical Center Utrecht (UMCU) in 1988–2007 for LGEA were invited as part of their clinical follow-up for interviews by pediatric pulmonologists and for lung function tests (LFT).

LGEA was defined as the impossibility to perform a direct end-to-end anastomosis because of the distance between the proximal and distal esophagus. One patient in de JI group underwent thoracoscopic traction of the two esophageal ends soon after birth, but because of leak at the distal esophagus traction was abandoned and esophageal replacement was performed. All the other patients primarily underwent GPU or JI.

Ethical statement

This assessment was conducted in accordance with the amended Declaration of Helsinki and the local UMCG Medical Ethics Review Board (Ref. M16.19177

Surgical procedures

GPU as popularized by Spitz et al.[5,11–14] was performed. Via a transverse laparotomy, a transhiatal posterior mediastinal tunnel was created. The stomach was brought up into the neck through the esophageal hiatus and the esophagogastric anastomosis was performed.

JI as popularized by Bax et al.[1–3] was performed. Via a median laparotomy, a pedicle graft was created by transecting the jejunum close to Treitz' ligament. The graft, with vascular pedicle, was brought through the posterior hiatus into the right chest where anastomoses were made between the proximal and distal esophagus and the graft (Figure 1).

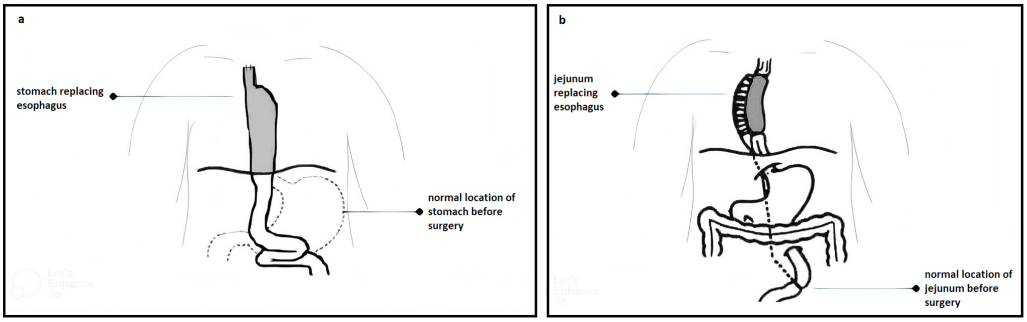


Figure 1 | Schematic representation of gastric pull-up and jejunal interposition. *(**b**) Adapted from "Long-term results of jejunal replacement of the esophagus," by Morihiro Saeki, Yoshiaki Tsuchida, Takashi Ogata et al., 1988. Journal of Pediatric Surgery, 1988;23:483–9. Copyright© 1988 Published by Elsevier Inc. Adapted with permission.*

Interviews

Data were collected prospectively using a prepared sheet of questions with the interviewer's opportunity to investigate specific themes in depth.
Anthropometric values, medication and diet at the time of interview were registered. Standard deviation scores for height/weight were calculated using growth charts for Dutch children with a deviation of more than −2 SD of the mean for age considered as abnormal[15].

LFT

Measurements were performed by certified technicians according to international consensus [16–17].

Results were compared and expressed as percentage of predicted values calculated on recent pediatric references for the Dutch population[18]. Percentiles b5th of predicted values (lower limit of normality, LLN = −1.96 z-scores) were considered as abnormal[19]. RV/TLC was considered abnormal when N95th percentile (upper limit of normality, ULN = +1.96 z-scores). For patients N18 years old EGKS(93) references were used[17].

A MasterScreen spirometer and body plethysmograph (Jaeger, Würzburg, Germany) were used in the GPU group. A Zan 100 spirometer (nSpire, USA) and a ZAN 500 Body USB (nSpire Health GmbH, Oberthulba Germany) were used in the JI group.

Values for forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), their ratio (FEV1/FVC), peak expiratory flow (PEF) were registered. At least three acceptable and repeatable maneuvers (conform ERS/ATS criteria) were required before recording any spirometric variable. The curve with largest sum of FVC and FEV1 was used for analysis. Abnormal FEV1/FVC was regarded as evidence of obstructive airway disease.

Residual volume (RV), total lung capacity (TLC) and their ratio (RV/ TLC) were examined using whole body plethysmography. Abnormal TLC was interpreted as evidence of a restrictive ventilatory defect, abnormal RV/TLC as air trapping.

Diffusion capacity was assessed with single breath carbon monoxide diffusion (DLCO). Mean DLCO was calculated from 2 measurements with maximal 10% difference. Abnormal DLCO corrected for TLC was regarded as reduced alveolocapillary diffusion, characteristic for parenchymal lung disease.

Endpoints

Primary endpoint was the lung function in patients after esophageal replacement, when compared to reference values obtained in healthy controls. Secondary endpoint was the difference between symptoms and lung function after GPU as compared to JI.

Statistics

A Mann–Whitney U test for continuous variables given a not normal distribution and Fisher's exact test for dichotomous variables (IBM SPSS Statistics 22) was used. P value b0.05 was considered as significant (two-tailed test).

RESULTS

Nine patients underwent GPU at the UMCG. Seven of them participated in the study (77%).
Fifteen children underwent JI at the UMCU. One of them died at the age of ten, most likely as a result of massive aspiration. Among the remaining fourteen patients eight (57%) participated (Table 1).
Median follow-up after surgery was 12 years [4–23]: 12 years [4–16] after GPU and 14 years [7–23] after JI.

There were no statistically significant differences concerning gestational age, birth weight, age at surgery and postoperative intensive care stay between participating and not participating subjects. Reasons for nonparticipation were unresponsiveness to invitation for follow-up or no-show at the outpatient clinic.

Table 1 | Characteristics of patients participating in the study and anthropometric values at the time of interview. Continuous variables are expressed as median (range)

	GPU (n=7)	**JI (n=8)**	**P value**
Male	*85% (6)*	*50% (4)*	0.28
Female	*15% (1)*	*50% (4)*	0.28
Gestational age (wk)	35 *(29-39)*	34 *(32-41)*	0.64
Birth weight (gr)	2280 *(1030-3040)*	2115 *(1480-3755)*	0.72
Age at surgery (days)	128 *(1-323)*	56 *(23-104)*	0.08
Type atresia			
- No fistula	71% *(5)*	12% *(1)*	0.41
- Proximal fistula	14% *(1)*	75% *(6)*	0.41
- Distal fistula	14% *(1)*	12% *(1)*	1
Congenital anomalies			
- Vertebral	57% *(4)*	12% *(1)*	0.11
- Anorectal	14% *(1)*	25% *(2)*	1
- Cardiac *	29% *(2)*	25% *(2)*	1
- Renal **	29% *(2)*	0% *(-)*	0.20
- Limbs	0% *(-)*	12% *(1)*	1
- Duodenal atresia	14% *(1)*	0% *(-)*	0.46
Anatomic tracheomalacia	71% *(5)*	87% *(7)*	0.56

Age (years)	12 (4-17)	14 (7-24)	0.64
Weight (Kg)	29 (16-50)	38 (23-60)	0.64
Height (cm)	146 (103-178)	160 (123-171)	0.64
BMI	15 (13-16)	15.5 (15-22)	0.83
Height/Age <-2SD	0% (-)	0% (-)	-
Weight/Age <-2SD	57% (4)	25% (2)	0.31
Weight/Height <-2SD	29% (2)	12% (1)	0.56

** atrial and ventricular septal defect, patent ductus arteriosus*

*** duplex collecting system, midline kidney*

Interviews

Respiratory symptoms were common (13/15). Chronic or recurrent cough (12/15) and dyspnea (9/15) were reported by the majority. Among the four GPU-patients who reported wheezing none had allergies. Three showed bronchial hyperresponsiveness at methacholine challenge test, the fourth patient showed reversible airways obstruction at forced oscillation technique. Two already used asthma medication at the time of interview.

Gastrointestinal symptoms were equally divided over both groups. One GPU-patient needed extra tube-feeding because of delayed gastric emptying. Growth was adequate in most JI-patients. GPU-patients showed appropriate length but were mostly underweight at time of interview. PPIs/H2-antagonists were used more often after GPU (Table 2).

Table 2 | Respiratory symptoms, episodic gastrointestinal symptoms, current tube feeding and medication use at time of interview. *RTIs: respiratory tract infections. ICS: inhalation corticosteroids.*

	GPU (n=7)	JI (n=8)	P value
Any cough	86% *(6)*	75% *(6)*	1
-continuous	43% *(3)*	37% *(3)*	1
-during infections	43% *(3)*	37% *(3)*	1
Any wheezing	57% *(4)*	0% *(-)*	0.02 (S)
-episodic wheezing	29% *(2)*	0% *(-)*	0.20
-during infection	29% *(2)*	0% *(-)*	0.20
Early childhood wheezing	29% *(2)*	12% *(1)*	0.56
Asthma-like symptoms -cough and wheezing	43% *(3)*	- *(0)*	0.07
Any dyspnea	57% *(4)*	62% *(5)*	1
-on exertion	57% *(4)*	25% *(2)*	0.31
-during infection	14% *(1)*	37% *(3)*	0.56
-during stress	0% *(-)*	12% *(1)*	1
Any noisy breathing	71% *(5)*	37% *(3)*	0.31
-continuous	0% *(-)*	25% *(2)*	0.46
-during infection	71% *(5)*	12% *(1)*	0.04 (S)
Early childhood noisy breathing	14% *(1)*	37% *(3)*	0.56

Apnea/cyanosis ever	29% *(2)*	- *(0)*	0.20
Recurrent pneumonia	14% *(1)*	25% *(2)*	1
Episodic pneumonia	14% *(1)*	25% *(2)*	1
Recurrent RTIs	29% *(2)*	37% *(3)*	1
Prophylactic Antibiotics	14% *(1)*	25% *(2)*	1
Beta -2 agonists	29% *(2)*	12% *(1)*	0.56
ICS	29% *(2)*	12% *(1)*	0.56
Dysphagia			
-currently	43% (3)	50% (4)	1
-in early childhood	14% (1)	37% (3)	0.56
Choking			
-currently	0% (-)	37% (3)	0.20
-in early childhood	14% (1)	12% (1)	1
Heartburn			
-currently	29% (2)	12% (1)	0.56
-in early childhood	14% (1)	25% (2)	1
Nausea	0% (-)	0% (-)	-

Vomit	14% (1)	12% (1)	1
Tube feeding	14% (1)	0% (-)	0.46
PPI/H2 antagonist	71% (5)	12% (1)	0.04 (S)
Prokinetics	14% (1)	12% (1)	1

LFT

One four years-old GPU-patient and one JI-patient with spastic diplegia were not able to perform LFT. In both groups all single LTF items were lower than in healthy controls. JI-patients demonstrated results closer to reference values for every LFT outcome when compared to GPU-patients. All six GPU-patients demonstrated obstruction and/or restriction vs 3/7 after JI (P = 0.07) (Table 3) (Figure 2).

Correlation between abnormalities at LFT and respiratory morbidity appears clinically more relevant in the GPU group (Table 4).

Table 3 | Results of lung function testing expressed both as percentage of predicted (%pred) and abnormal values: < 5th percentile (< LLN = -1.96 z-scores). RV/TLC was considered abnormal when > 95th percentile (>ULN = +1.96 z-scores). Continuous variables are expressed as median (range)

%pred	GPU (n=6)	JI (n=7)	P value
FEV1/FVC	**85** *(81-105)*	**92** *(74-104)*	0.94
-abnormal	*67% (4)*	*29% (2)*	0.28
FEV1	**62.5** *(52-73)*	**80** *(43-88)*	0.39
-abnormal	100% *(6)*	71% *(5)*	0.46
FVC	**65.5** *(54-89)*	**83** *(58-95)*	0.43
-abnormal	83% *(5)*	43% *(3)*	0.26

PEF -abnormal	**52.5** *(47-67)* 100% *(6)*	**74** *(40-84)* 43% *(3)*	0.08 0.07
TLC -abnormal	**80.5** *(71-98)* 67% *(4)*	**91** *(62-103)* 29% *(2)*	0.28 0.28
RV/TLC -abnormal	**126** *(113-166)* 17% *(1)*	**122** *(95-193)* 43% *(3)*	0.66 0.56
DLCO -abnormal	**75** *(62-100)* * 40% *(2)*	**89** *(73-119)* 29% *(2)*	0.28 1

** evaluated in 5 patients*

Table 4 | Symptoms reported by patients with LFT suggestive for restrictive ventilatory disorder (TLC < LLN) and patients with LFT suggestive for obstructive ventilatory disorder (FEV1/FVC < LLN)

TLC < LLN	**GPU (n=4)**	**JI (n=2)**	**P value**
Any dyspnea	75% *(3)*	- *(0)*	0.4
Any cough	100% *(4)*	- *(0)*	0.06
FEV1/FVC < LLN	**GPU (n=4)**	**JI (n=2)**	
Asthma like symptoms	75% *(3)*	- *(0)*	0.4
Any noisy breathing	100% *(4)*	- *(0)*	0.06

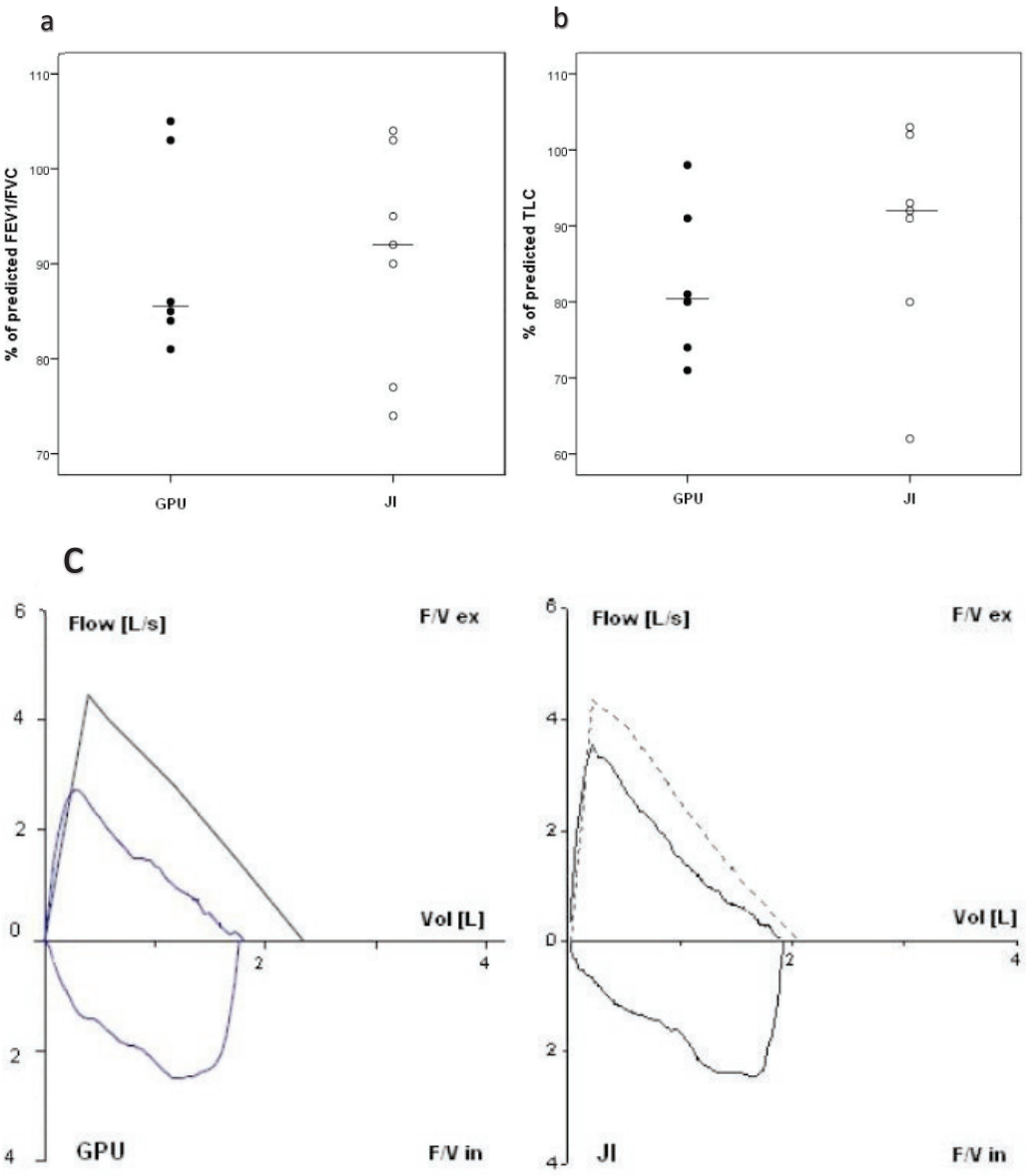


Figure 2a.b.c

*(**a**)Forced Expiratory Volume in the first second/Forced Vital Capacity as percentage of predicted values. Median FEV1/FVC after GPU 85 (81-105), after JI 92 (74-104), P = 0.94*

*(**b**) Total Lung Capacity as percentage of predicted values. Median TLC after GPU 80.5 (71-98), median TLC after JI 91 (62-103), P = 0.28*

*(**c**)Typical flow/volume loop after GPU and JI registered during spirometry, both in 11 years old patients*

Spirometry

Overall measured volumes were lower in patients compared to controls. Six of thirteen patients showed evidence of obstructive ventilator disorder. In the JI group reported volumes were closer to normal values than in the GPU group.

Body plethysmography

Overall TLC was reduced compared to controls. Six of thirteen patients showed restrictive ventilatory disorder. TLC was decreased in the majority of GPU-patients, in contrast to measurements after JI. More JI-patients showed evidence for air-trapping.

Single breath CO diffusion

DLCO corrected for TLC was normal for all subjects. However, DLCO was lower after GPU compared to JI.

DISCUSSION

This paper reports long-term follow-up of respiratory morbidity and lung function after esophageal replacement surgery in children suffering from LGEA. Specifically,
we compare respiratory outcome after GPU and JI. Our findings show that respiratory complaints after esophageal replacement are frequent and appear clinically relevant. Lung function was impaired when compared to healthy controls. Respiratory symptoms tended to occur more frequently after GPU but were also observed in the majority of JI-patients. GPU-patients showed a decrease in TLC when compared to JI-patients and lung function parameters in JI-patients were closer to reference values compared to GPU

Respiratory symptoms

Respiratory symptoms are common in EA-repair patients[20]. A reduction of symptoms as children reach adolescence has been suggested[21]. However, in adults respiratory-related quality of life is lower and daily respiratory problems are more common than among controls [10]. Prevalence of patients suffering from respiratory complaints at follow-up is 11%–57%[10,20–23]. In a recent meta-analysis a pooled estimated prevalence of persistent respiratory symptoms in 593 EA-repair patients aged 10–59 years was performed. Most reported symptoms were wheezing (35%), respiratory tract infections (24%), doctor-diagnosed asthma (22%) and persistent cough (14%)[24].

As in EA-repair patients, our findings indicate a considerable prevalence of respiratory symptoms after esophageal replacement for LGEA. Notably the children in the present study did not suffer from severe congenital lung problems and were not more premature than seen in EA patients. Respiratory symptoms were widely reported at follow-up (13/15). LGEA-patients show a higher prevalence of respiratory morbidity compared to healthy subjects of similar age when a recent nation-wide survey conducted by general practitioners among Dutch children is used (recurrent respiratory tract infections 33% vs 9%, cough 80% vs 6%, dyspnea 60% vs 5%, asthma-like symptoms 20% vs 4%)[25].

Most patients (9/15) were diagnosed with a tracheoesophageal fistula (TEF). We consider anatomic tracheomalacia an obligate finding in children with TEF, because of loss of cartilage in the correspondent tract of tracheal wall, however this is not necessarily clinically symptomatic. In three patients without TEF, tracheomalacia was also either diagnosed by laryngotracheoscopy (one) or clinically suspected (two). No patients in our study underwent aortopexy. Chronic cough, dyspnea, wheezing and noisy breathing might be a consequence of the expiratory airways collapse promoted by tracheal cartilage weakness[26,27].

Gastrointestinal symptoms

Gastrointestinal symptoms were less frequently reported than respiratory problems. A relation between gastroesophageal reflux disease (GERD) with subsequent (micro) aspiration and respiratory deterioration in EA-repair patients has been postulated[9]. Not every patient in our study underwent pH-metry. Nevertheless, our data indicate a modest prevalence of GERD symptoms (3/15 patients, 20%) compared to EA-repair patients (40%)[24]. However gastroesophageal reflux might be present subclinically. This should be considered in the follow-up of LGEA-patients.

Pulmonary function

The incidence of ventilatory disorders in EA-repair patients varies widely. Differences in the definition of obstruction/restriction might be a contributing factor. There is consensus however that lung function impairment persists into adulthood. Agrawal et al.[28] reported a mean reduction of FVC and total gas volume exceeding −2 SD, suggestive for restrictive disorder in 14 children aged 7–12 years. Beucher et al.[29] found abnormal LFT in 21/31 children aged 7–13 years, with restriction in 7/31 (23%) and obstruction in 6/31 (19%). Malmström et al. performed spirometry in 31 patients aged 10–20 years and found restriction in 32% and obstruction in 30%. An Australian study including 155 patients aged 6–37 years showed obstructive disorders in 25% and restrictive disorders in 18%[21]. Finally, Sistonen et al.[10] collected spirometry data from 101 adults aged 22–56 years: 78% showed abnormal values. Restriction and obstruction were equally distributed (both 21%) and 36% had a mixed condition. Recently 7 LGEA-patients underwent LFT at 7 years old: 42% showed obstruction and 28% restriction. However, no GPU or JI was performed in these patients and most of them underwent delayed primary end-to-end anastomosis after multiple months[8]. Interpretation of LFT is highly dependent on reference equations[18]. Those used for our study were obtained from a random sample of Caucasian children aged 2–18 years and are appropriate for the current Dutch pediatric population. Contrarily to previous references, sex/ age/height and their interaction are included as determinants resulting in better fitting reference equations[30,31].
Our findings indicate that respiratory function after esophageal replacement for LGEA is impaired compared to healthy controls. Pulmonary function in LGEA-patients seems to be worse than in EA-patients. We found abnormal LFT values for 12/13 patients. All single LFT components were lower than reference values. Evidence for restrictive and obstructive ventilatory disorder was present in 6/13 patients in each group.

Comparison of GPU and JI

Respiratory symptoms occurred more frequently after GPU. Wheezing was significantly more recorded after GPU. No wheezing or asthma-like symptoms (combination of wheezing and cough) were recorded in JI-patients at all. We reported wheezing as a symptom and not necessarily as related to asthma, however a potential trigger for asthma-like symptoms after GPU may lie in a higher prevalence of GERD. Heartburn was reported equally, but more GPU-children used PPIs/H2-antagonists. This should be interpreted as a procedure-related prevention. Multiple factors have been advanced as predisposing to reflux after gastric mobilization in the mediastinum: gastroesophageal junction displacement with loss of the His angle, delayed gastric emptying, the negative intra-thoracic pressure and the positive intraluminal pressure in the transposed stomach[32,33]. A possible relation should be investigated infurther studies, including pH-metry.

Dyspnea on exertion after GPU was reported twice as often as after JI. It is important to realize that the patients' adaptation to reduced lung capacity during growth might lead to subjective underestimation of symptoms when surveilling these children.

Infrequent respiratory problems in 24 JI-children after a median follow-up of 5.5 years have been described by Bax and van der Zee[2]. However, lung function and respiratory morbidity were not investigated systematically. Part of our patients belongs to the same cohort. In accordance with that study, respiratory complaints after JI seem not prominent, even after a longer follow-up and interviews with pediatric pulmonologists.

The majority of GPU-patients showed a restrictive ventilatory disorder pattern with low TLC and FVC. Every patient had abnormal PEF. FEV1/FVC after GPU was lower than in controls but flow-volume loops reveal airway obstruction in a few patients only. These findings are in line with those of Davenport et al.[33] who in 1996 investigated respiratory function after GPU for LGEA in 16 children (median age 9 years). The observed restrictive ventilatory defects, caused by decreased lung volumes after GPU, could be explained by the presence of a space-occupying organ in the thorax which may limit normal lung growth (relative hypoplasia). This may lead to reduced exercise capacity. Exercise testing could further validate this finding.

Although a subject of debate, some have suggested that reduced lung volumes in prematures might improve dramatically with somatic growth during early childhood (catch-up) and proceed normally thereafter[34,35]. Whether the intrathoracic stomach may influence this lung remodeling process in the first years of life remains a question. The restrictive ventilatory disorder may also be related to active damage of lung tissues promoted by the transposed stomach. Reflux and prolonged (micro) aspiration in the airways may cause chronic pulmo-nary inflammation, potentially progressing to fibrosis[36]. However, diffusion abnormalities were not measured in both groups.

The majority of JI-patients (4/7) had no evidence for either obstructive or restrictive disorders. Both median FEV1/FVC and TLC appear close (N 90% of predicted) to reference values. The abnormalities found are heterogeneous which suggests the absence of a specific procedure-related pulmonary disorder after JI. Overall LFT suggest that esophageal replacement by GPU affects respiratory volumes more than JI.

Main limitation of this study is the small sample size, which is inevitable since it reflects the low number of patients with LGEA (one in 40,000 live births). Because of these limited numbers, comparison between GPU and JI is challenging and the observed differences between the groups were not statistically significant. Therefore, the character of this study is mainly descriptive. However, we think the hypotheses we were able to postulate are worth investigating in future studies.

Follow-up

Follow-up after esophageal replacement surgery has a multidisciplinary character. In this context longitudinal respiratory assessment is important, especially when considering transition into adulthood and adult healthcare. Restrictive ventilatory disorders with reduced exercise capacity might benefit from pulmonary physiotherapy or training programs. We suggest that, in case of asthma-like symptoms, bronchial hyperresponsiveness should be promptly investigated, especially when the possibility of (repeated) gastro-esophageal reflux is considered. Finally, it is important to give adequate support to patients and their families when respiratory symptoms which may influence their quality of life are involved.

CONCLUSION

Children who underwent esophageal replacement for LGEA have relevant lung morbidity and impaired respiratory function when compared to healthy controls. Patients after JI seem to have less symptoms and better lung function than patients after GPU. Patients after GPU mainly have a restrictive ventilatory disorder, which could be related to the space-occupying organ in the chest. Respiratory follow-up into adult life is important after esophageal replacement surgery.

REFERENCES

1 Bax NMA, M. H. Riivekamp, A. J. Pull ter Gunne, and D. C. van der Zee. Early one-stage orthotopic jejunal pedicle-graft interposition in long-gap esophageal atresia. Pediatr Surg Int (1994) 9: 483-485

2 Bax NMA, van der Zee DC. Jejunal pedicle grafts for reconstruction of the esophagus in children. J Pediatr Surg 2007;42(2):363-369

3 Bax NMA. Jejunum for bridging long-gap esophageal atresia. Semin Pediatr Surg. 2009 Feb;18(1):34-9. doi: 10.1053/j.sempedsurg.2008.10.007

4 Hamza AF. Colonic replacement in cases of esophageal atresia. Semin Pediatr Surg 2009;18(1):40–43

5 Spitz L. Gastric transposition for esophageal substitution in children. J Pediatr Surg. 1992 Feb;27(2):252-7; discussion 257-9. Review.

6 Gallo G, Zwaveling S, Groen H, Van der Zee D, Hulscher J. Long-gap esophageal atresia: a meta-analysis of jejunal interposition, colon interposition, and gastric pull-up. Eur J Pediatr Surg 2012;22 (6):420–425

7 Gallo G, Zwaveling S, Van der Zee DC, Bax NMA, de Langen ZJ, Hulscher JBF. A two-center comparative study of gastric pull up and jejunal interposition for long-gap esophageal atresia. J Pediatr Surg. Epub 2014 Jul 11. doi: 10.1016/j.jpedsurg.2014.05.026

8 Jönsson L, Friberg LG, Gatzinsky V, Kötz K, Sillén U, Abrahamsson K. Treatment and Follow-Up of Patients with Long-Gap Esophageal Atresia: 15 Years' of Experience from the Western Region of Sweden. Eur J Pediatr Surg 2015 Jan 5. In press. doi: 10.1055/s-0034-1396415

9 Olbers J, Gatzinsky V, Jönsson L, Friberg LG, Abrahamsson K, Sillén U, Gustafsson P. Physiological Studies at 7 Years of Age in Children Born with Esophageal Atresia. Eur J Pediatr Surg. 2014. In press doi: 10.1055/s-0034-1390017

10 Sistonen S, Malmberg P, Malmström K, Haahtela T, Sarna S, Rintala RJ, Pakarinen MP. Repaired oesophageal atresia: respiratory morbidity and pulmonary function in adults. Eur Respir J. 2010 Nov;36(5):1106-12

11 Spitz L. Gastric transposition via the mediastinal route for infants with long-gap esophageal atresia. J Pediatr Surg. 1984 Apr;19(2):149-54

12 Spitz L. Gastric transposition for oesophageal replacement. Pediatr Surg Int. 1996 Apr; 11(4):218-20. doi: 10.1007/BF00178420.

13 Spitz L Kiely E, Pierro A Gastric transposition in children--a 21-year experience. J Pediatr Surg. 2004 Mar; 39(3):276-81; discussion 276-81.

14 Spitz L Gastric transposition in children. Semin Pediatr Surg. 2009 Feb;18(1):30-3. doi: 10.1053/j.sempedsurg.2008.10.006

15 Growth curves calculated by Growth Analyser according to Dutch Growth Research Foundation (DGRF) https://growthanalyser.org/about-us/dutch-growth-research-foundation/

16 American Thoracic Society. Standardization of spirometry—1987 update. Official statement of American Thoracic Society. Respir Care 1987;32: 1039–1060

17 Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl 1993;16:5–40.

18 Koopman M. Zanen P, Kruitwagen CL, van der Ent CK, Arets HG.. Reference values for paediatric pulmonary function testing: The Utrecht dataset. Respir Med. 2011 Jan;105(1):15-23. doi: 10.1016/j.rmed.2010.07.020

19 Quanjer PH, Interpreting spirometric results: The Z-Score. Resp Mir 2013 Sept, Volume III, Issue IV

20 Sadreameli S, McGrath-Morrow S, Respiratory care of Infants and Children with Congenital Tracheo-Oesophageal Fistula and Oesophageal Atresia Paediatr Respir Rev. 2015 Mar 3. doi: 10.1016/j.prrv.2015.02.005

21 Chetcuti P, Phelan P D. Respiratory morbidity after repair of oesophageal atresia and tracheoesophageal fistula. Arch Dis Child 1993;68167–170.170

22 Taylor AC, Breen KJ, Auldist A, Catto-Smith A, Clarnette T, Crameri J, Taylor R, Nagarajah S, Brady J, Stokes K. Gastroesophageal reflux and related pathology in adults who were born with esophageal atresia: A long-term follow-up study. Clin Gastroenterol Hepatol 2007; 5: 702–6.

23 Malmström K, Lohi J, Lindahl H, Pelkonen A, Kajosaari M, Sarna S, Malmberg LP, Mäkelä MJ. Longitudinal follow-up of bronchial inflammation, respiratory symptoms, and pulmonary function in adolescents after repair of esophageal atresia with tracheoesophageal fistula. J Pediatr 2008;153:396-401

24 Connor MJ, Springford LR, Kapetanakis VV, Giuliani S. Esophageal atresia and transitional care –step 1: a systematic review and meta-analysis of the literature to define the prevalence of chronic long-term problems. Am J Surg. 2015;209,747-759

25 M.W. van der, Suijlekom-Smit, L.W.A. van, Schellevis, van der Wouden L.C. Tweede Nationale Studie naar ziekten en verrichtingen in de huisartspraktijk: het kind in de huisartspraktijk. Utrecht, NIVEL, 2005. http://www.nivel.nl/sites/default/files/bestanden/ns2-kind-in-de-huisartspraktijk.pdf

26 Doshi J, Krawiec ME. Clinical manifestations of airway malacia in young children. J Allergy Clin Immunol. 2007 Dec;120(6):1276-8.

27 Pan W, Peng D, Luo J, Liu E, Luo Z, Dai J, Fu Z, Li Q, Huang Y. Clinical features of airway malacia in children: a retrospective analysis of 459 patients Int J Clin Exp Med 2014;7(9):3005-3012

28 Agrawal L, Beardsmore CS, MacFadyen UM. Respiratory function in childhood following repair of oesophageal atresia and tracheoesophageal fistula. Archives of disease in childhood 1999;81:404–8.

29 Beucher J, Wagnon J, Daniel V, Habonimana E, Fremond B, Lapostolle C, Guillot S, Azzis O, Dabadie A, Deneuville E. Long-term evaluation of respiratory status after esophageal atresia repair. Pediatr Pulmonol 2013; 48: 188–194.

30 Quanjer PH, Borsboom GJ, Brunekreef B, Zach M, Forche G, Cotes JE, Sanchis J, Paoletti P. Spirometric reference values for white European children and adolescents: polgar revisited. Pediatr Pulmonol 1995;19:135-42.

31 Stanojevic S, Wade A, Stocks J, Hankinson J, Coates AL, Pan H, Rosenthal M, Corey M, Lebecque P, Cole TJ. Reference ranges for spirometry across all ages: a new approach. Am J Respir Crit Care Med 2008;177:253-60

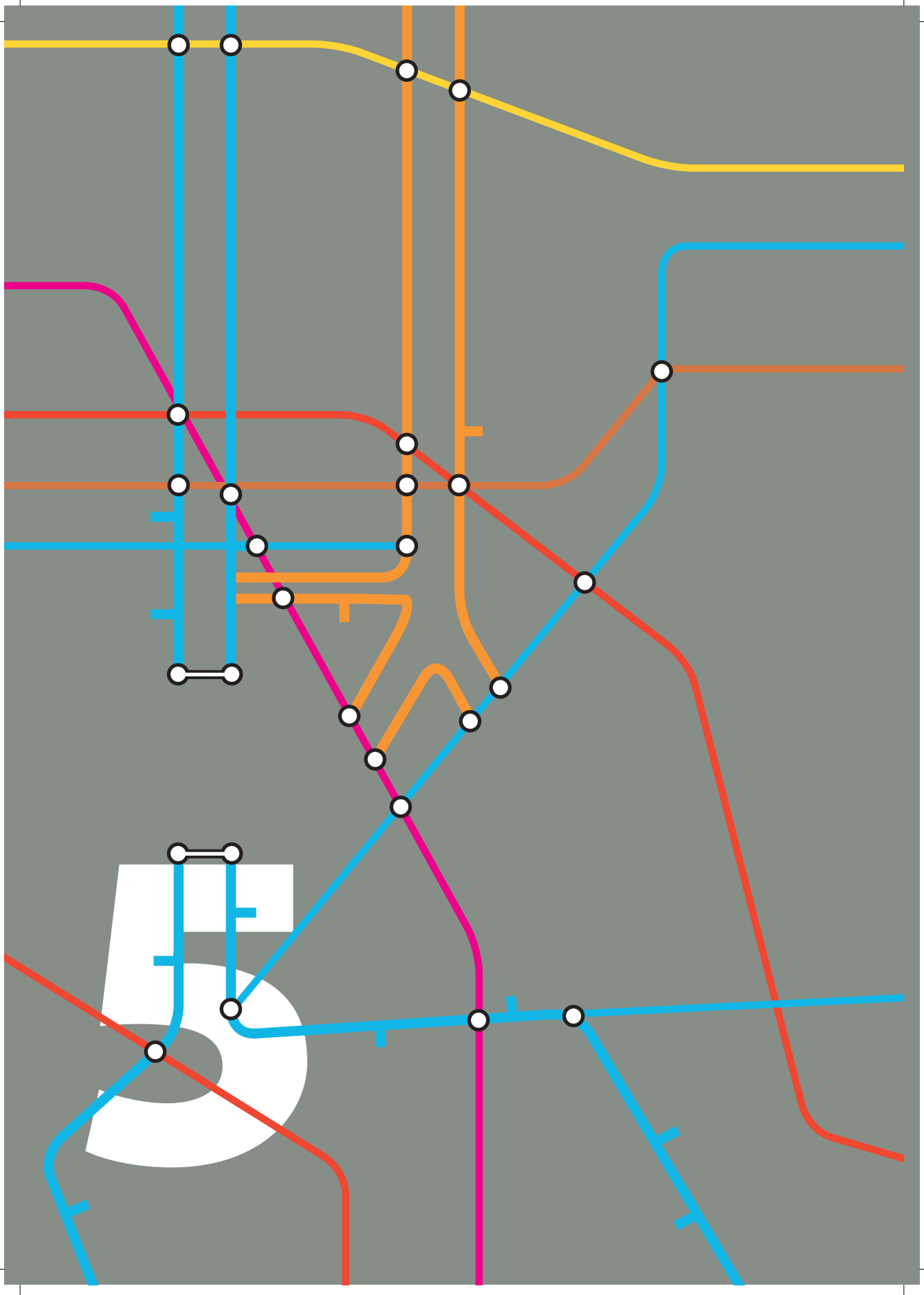
32 Jamieson G.G, Reflux after oesophagectomy. Br J Surg. 2004 Feb;91(2):137-41

33 Davenport M, Hosie GP, Tasker RC, Gordon I, Kiely EM, Spitz L. Long-term effects of gastric transposition in children: A physiological study. J Pediatr Surg 1996;31:588-93

34 Koumbourlis AC, Motoyama EK, Mutich RL, Mallory GB, Walczak SA, Fertal K. Longitudinal follow-up of lung function from childhood to adolescence in prematurely born patients with neonatal chronic lung disease. Pediatr Pulmonol 1996;21:28–34

35 Friedrich L, Pitrez PM, Stein RT, Goldani M, Tepper R, Jones MH. Growth rate of lung function in healthy preterm infants. Am J Respir Crit Care Med 2007; 176:1269–1273.

36 Schachter L, Dixon J, Pierce R, O'Brien P. Severe Gastroesophageal Reflux Is Associated With Reduced Carbon Monoxide Diffusing Capacity. Chest. 2003 Jun;123(6):1932-8



CHAPTER 5

Graft dilatation and Barrett's esophagus in adults after esophageal replacement in long-gap esophageal atresia

Eleonora S van Tuyll van Serooskerken, Gabriele Gallo, Bas LAM Weusten, Jessie Westerhof, Lodewijk AA Brosens, Sander Zwaveling, Johannes W Verweij, Jan BF Hulscher, Hubertus GM Arets, Arnold J.N. Bittermann, David C van der Zee, Stefaan HAJ Tytgat*, Maud YA Lindeboom*

*shared last author

Submitted

ABSTRACT

Background
Esophageal replacement (ER) with gastric pull-up (GPU) or jejunal interposition (JI) used to be the standard treatment for long-gap esophageal atresia (LGEA). Changes of the ER grafts on a macro- and microscopic level however, are unknown.

Aim
This study aims to evaluate long-term clinical symptoms and anatomical and mucosal changes in adolescents and adults after ER for LGEA.

Methods
A cohort study was conducted including all LGEA patients ≥16 years who had undergone GPU or JI between 1985-2003 at two tertiary referral centers in the Netherlands. Patients underwent clinical assessment, contrast study and endoscopy with biopsy. Data was collected prospectively. Group differences between JI and GPU patients, and associations between different outcome measures were assessed using the Fisher's exact test for bivariate variables and the Mann-Whitney U-test for continuous variables. Differences with a p-value <0.05 were considered statistically significant.

Results
Nine GPU patients and eleven JI patients were included. Median age at follow-up was 21.5 years and 24.4 years, respectively. Reflux was reported in six GPU patients (67%) vs four JI patients (36%) (p=0.37). Dysphagia symptoms were reported in 64% of JI patients, compared to 22% of GPU patients (p=0.09). Contrast studies showed dilatation of the jejunal graft in six patients (55%) and graft lengthening in four of these six patients. Endoscopy revealed columnar-lined epithelium esophagus in three GPU patients (33%) and intestinal metaplasia was histologically confirmed in two patients (22%). No association was found between reflux symptoms and macroscopic anomalies or intestinal metaplasia. Three GPU patients (33%) experienced severe feeding problems versus none in the JI group. The median BMI of JI patients was 20.9 kg/m2 versus 19.5 kg/m2 in GPU patients (p=0.08).

Conclusion
The majority of GPU patients had reflux and intestinal metaplasia in 22%. The majority of JI patients had dysphagia and a dilated graft. Follow-up after ER for LGEA is important

INTRODUCTION

Long-gap esophageal atresia (LGEA) is present in approximately 10% of all esophageal atresia (EA)[1] and remains a surgical challenge[2,3]. Preservation of the native esophagus in LGEA is the treatment of choice, which can be accomplished by delayed primary anastomosis[4,5] or elongation techniques[6–10] in experienced centers. Previously however, almost all LGEA patients underwent esophageal replacement (ER) with gastric[11], jejunal[12] or colonic[13] conduit. Since survival rates have improved up to 90% in EA[14], focus has shifted to the investigation and treatment of long-term morbidities and quality of life. Gastrointestinal symptoms, including gastroesophageal reflux (GER) and dysphagia, are frequent in EA[15]. The incidence of (severe) reflux is expected to be even higher in patients after a gastric pull-up (GPU)[16]. This may be explained by mobilization of the stomach into the mediastinum. This results in alteration of the shape of the gastroesophageal junction and consequently the loss of the Angle of His, which is one of the anti-reflux barriers. Moreover, the negative intrathoracic pressure and the positive intraluminal pressure in the transposed stomach may increase GER[17]. Micro-aspiration due to GER may contribute to chronic cough and asthma-like symptoms[18,19]. Chronic GER may lead to esophageal mucosal alterations with a four times higher incidence of Barrett's esophagus compared to healthy controls[20]. Literature on the long-term outcome of ER is scarce[16,21–23]. Studies on long-term endoscopic findings in LGEA patients are lacking.

Therefore, this study aims to evaluate the long-term outcome of jejunal interposition (JI) and GPU on clinical symptoms and anatomical and mucosal changes in adolescents and adults after LGEA.

METHODS

Study design and participants

A cohort study was conducted including all LGEA patients ≥16 years old who had undergone JI or GPU at the University Medical Center Utrecht (UMCU) and the University Medical Center Groningen (UMCG) between 1985 and 2003. As of 2018, all 17-year-old EA patients are routinely referred to the gastroenterologist for clinical assessment and endoscopic and histologic screening for esophageal mucosal lesions. All adult LGEA patients (>17 years), that were not yet included in the routine follow-up, were invited for screening. Patients that had ER for LGEA underwent a one-time barium contrast study, to evaluate the anatomy of the graft. Data was collected prospectively. Gastroscopies that were performed after the age of 17 years and within the last four years, were reviewed retrospectively.

Surgical procedures

All esophageal replacements had been performed by experienced pediatric surgeons. JI was performed as described by Bax et al[12,24,25]. The GPU was performed as previously described by Spitz et al[11,26].

Clinical assessment

Baseline characteristics, including gender, age, type of EA and associated anomalies were obtained from the electronic medical records.

Gastrointestinal symptoms

Gastrointestinal symptom assessment (e.g. reflux, dysphagia) was derived from the routine outpatient follow-up at the Gastroenterology Department.

Contrast study

Upper gastrointestinal barium contrast studies were analyzed by an experienced radiologist and pediatric surgeon for the following parameters: anastomotic stenosis, stasis of contrast, reflux, graft-dilatation and graft-lengthening (resulting in a siphon shaped graft) of the JI and the position of the stomach in GPU patients.

Upper endoscopy and histology

Upper endoscopy was performed by a gastroenterologist to assess the esophagus, the anastomotic site(s), the grafts, the gastroesophageal junction and the stomach. Reflux esophagitis and intestinal metaplasia were scored according to the Los Angeles (LA) classification[27] and Prague criteria[28]. Barrett's esophagus was defined as columnar lined esophagus on endoscopy in combination with intestinal metaplasia (IM) on histology. In patients with JI, biopsies were taken from both the distal and proximal esophagus. Jejunal grafts were evaluated on proximal or distal stenosis, (distal) dilatation of the graft and on macroscopic lesions. Biopsies of the jejunal graft were taken if mucosal abnormalities were present. The GPU was evaluated on anastomotic stenosis, macroscopic lesions and altered anatomy. In patients with GPU, biopsies were taken just proximal to the anastomosis. In case of macroscopic abnormalities of the GPU, biopsies were taken. Endoscopies were reviewed by an experienced gastroenterologist and a pediatric surgeon. Biopsies were evaluated for inflammation, eosinophilia and metaplasia by the Pathology Department by an expert gastrointestinal pathologist.

Ethical approval

This study was part of a larger cohort study on the long-term outcome in LGEA patients. The study protocol was submitted to the UMCU Ethics Committee (METC 18-458/C). According to the Medical Research Involving Human Subject Act, no ethical approval was required.

Statistical Analysis

Continuous skewed variables were presented as median and range, categorical data were presented as frequencies and percentage. Group differences between JI and GPU patients, and associations between different outcome measures were assessed using the Fisher's exact test for bivariate variables and the Mann-Whitney U-test for continuous variables. Differences with a p-value <0.05 were considered statistically significant. The analyses were performed using SPSS for Windows, version 25.0 (IBM Corp., Armonk, NY).

RESULTS

Between 1985 and 2003, a total of 24 patients underwent ER for LGEA (Figure 1). One JI patient was deceased at the age of 10 years due to massive aspiration. After following the exclusion criteria, twenty patients were included in this study. Nine patients underwent GPU and eleven underwent JI. Median age at follow-up was 21.5 years (range 20.2-34.1) for GPU patients and 24.4 years (range 16.1-31.2) for JI patients. Five JI patients (46%) and all GPU patients were male (p=0.01). Associated anomalies (e.g. cardiac, renal, musculoskeletal anomalies) were more present in GPU patients than in JI patients (100% vs. 55%, p=0.04). In both groups severe mental retardation and Down Syndrome were present in one patient. Preoperative gastrostomy was present in all JI patients and in eight (89%) GPU patients. Anastomotic strictures requiring dilatation had developed in eight JI patients (73%) and five GPU patients (55%). Fundoplication was required in one JI patient at the age of 2 years. Patient characteristics are shown in Table 1.

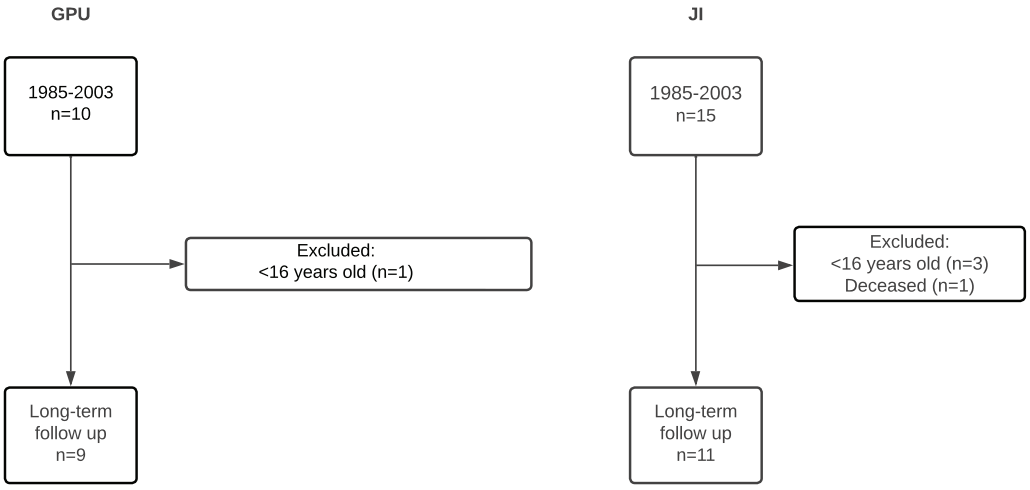


Figure 1 | Flowchart of patients included in the study

Table 1 | Patient characteristics GPU & JI

Value	GPU (n=9)	JI (n=11)	p-value
Male	9 (100%)	5 (46%)	0.01*
Gestational age (weeks)	33.9 (29-39)	34.7 (32.3-41.3)	0.15
Premature	7 (78%)	8 (73%)	1.0
Birthweight (grams)	1680 (1030-3040)	2010 (1115-3755)	0.49
Gross type EA			0.63
A	5 (56%)	4 (36%)	
B	3 (33%)	6 (55%)	
C	1 (11%)	1 (9%)	
Associated anomalies[a]	9 (100%)	6 (55%)	0.04*
Down's syndrome	1 (11%)	1 (9%)	
Anaorectal malf.	1 (11%)	1 (9%)	
Duodenal atresia	1 (11%)	1 (9%)	
Musculoskeletal	4 (44%)	3 (27%)	
Cardiac	1 (11%)	2 (18%)	
Renal anomaly	4 (44%)	1 (9%)	
Palatoschisis	2 (22%)	0	

All data are presented as median (range) or n (%)

[a]Some patients have multiple anomalies

**Indicating statistical significance*

Table 2 | GI outcome in GPU & JI

Variable	GPU (n=9)	JI (n=11)	p-value
Age at surgery (d)	128 (1-323)	67 (41-149)	0.21
Gastrostomy (n,%)	8 (89%)	11 (100%)	0.45
Fundoplication (n,%)	0	1 (9.1%)	1.0
Stenosis[a] (n,%)	5 (56%)	8 (73%)	0.64
Dilatations total (n)	3 (1-4)	3 (1-15)	0.76
Dilatations within 1st year (n)	1 (1-3)	2.5 (0-15)	0.26

[a]Stenosis requiring intervention

Data are presented as median (range) or n (%)

Clinical assessment

Reflux complaints were reported in six of the nine GPU patients (67%) and in four out of 11 JI patients (36%) (p=0.37). Dysphagia symptoms were scored in seven JI patients (64%) versus two GPU patients (22%) (p=0.09).

Three GPU patients (33%) experienced severe feeding problems. Due to swallowing disabilities, one patient was still fully dependent on gastrostomy feeding, with minimal attempts of liquid oral feeds. Another patient required additional jejunostomy feeding until the age of 21 years but has recently reached a full oral diet. One patient required additional drink nutrition to achieve a full oral diet. In the JI group, no severe feeding problems were observed.

The median BMI of JI patients was 20.9 kg/m2 (range 17.9-27.6) versus 19.5 kg/m2 (range 17.5-21.6) in GPU patients (p=0.08). Two JI patients (18%) were underweight (BMI <18.5 kg/m2) and one patient was overweight (BMI >25 kg/m2). Three GPU patients (33%) were underweight, none of the patients were overweight.

Table 3 | Clinical data

Variable	GPU (n=9)	JI (n=11)	p-value
Age at follow-up (median, years)	21.5 (20.2-34.1)	24.4 (16.1-31.2)	0.85
GER complaints	6 (67%)	4 (36%)	0.37
Dysphagia	2 (22%)	7 (64%)	0.09
FOIS			
-Total oral diet with no restrictions	5	5	
-Specific food limitations	1	2	
-Multiple consistencies, requiring special preparation	1	0	
-Tube-dependent	1	0	
-Missing	1	4	
PPI use	4 (44%)	3 (27%)	0.38
BMI (kg/m^2)	19.5 (17.5-21.6)	20.9 (17.9-27.6)	0.08

Data are presented as median (range) or n (%)

CONTRAST STUDY

GPU

Barium contrast studies were performed in five of the nine GPU patients (56%). In one patient, the stomach was completely transposed into the thorax. This patient showed some lengthening of the distal esophagus and stasis of liquids in the distal esophagus. Another patient, with Down Syndrome, also showed stasis of contrast in the esophagus. No reflux was observed in these patients.

Four out of nine GPU patients did not undergo a contrast study; three patients did not consent because they did not experience major gastrointestinal complaints. One patient with mental retardation was unable to perform a contrast study due to severe swallowing difficulties.

JI

Barium contrast studies were performed in all 11 JI patients. Ten patients (91%) showed stasis of contrast in the ER graft. None of the patients had a proximal or distal stenosis. The jejunal graft was dilated in six (55%) patients. In two of these patients, graft dilatation was severe. In four of these six patients, mild to moderate lengthening of the distal part of the jejunal graft was observed (Figure 2).

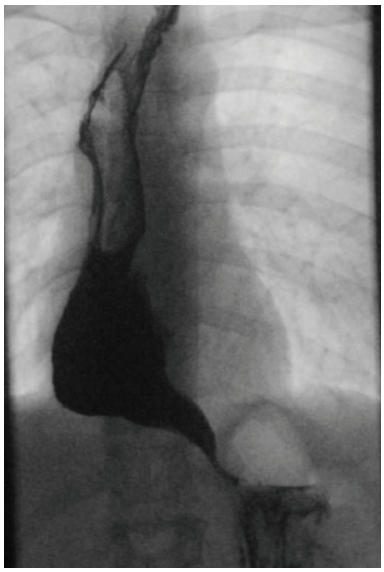


Figure 2 | Lengthening and dilatation of the distal jejunal graft

ENDOSCOPIC RESULTS

GPU

All GPU patients (n=9) had undergone gastroscopy. The median distance from the incisors to the anastomosis was 19cm (range 17-24). Macroscopic anomalies of the native esophagus were seen in five patients (56%); three patients showed columnar lined esophagus (33%) (C0M2, C0M2, C1M2) (Figure 3). One patient had an erosion at the distal part of the esophagus and another patient, who was gastrostomy dependent due to severe swallowing difficulties, had a pinpoint stenosis of the anastomosis.

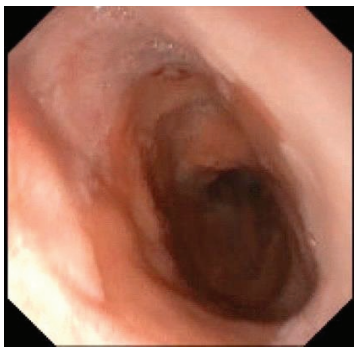


Figure 3 | Barrett's esophagus (C0M2) in a GPU patient

JI

All JI patients (n=11) had undergone upper endoscopy. The median distance from the incisors to the proximal anastomosis was 21cm (range 18-25), the median length of the jejunal graft was 15cm (range 12-22) and the median length of the distal esophagus was 4.5cm (range 0-8). In none of the patients a proximal or distal anastomotic stenosis was present. Macroscopic anomalies were seen in five patients (45%): two patients showed macroscopic esophagitis according to the LA classification (grade A, n=1; grade B, n=1), one patient had fields of squamous epithelium in the proximal part of the jejunal graft, one patient showed elevation of normal mucosa in the distal esophagus and a neurological impaired patient had stasis of food and an ulcer at the distal part of the jejunal graft. None of the JI patients showed columnar lined esophagus.

HISTOLOGIC RESULTS

GPU

In three patients with macroscopic columnar-lined esophagus, biopsies of the native distal esophagus showed intestinal metaplasia in two patients (22%), both with Prague classification C0M2 (2 men; median age 21.6 years). In two patients, biopsies of the distal esophagus showed chronic inflammation. Biopsies in another two patients showed hyperplastic squamous epithelium without dysplasia. In one patient, histopathology revealed that biopsies of cardia and corpus were obtained. Histopathology showed no signs of dysplasia in any of the patients. In one patient without macroscopic anomalies, no biopsies specimens were taken.

JI

In three patients, histology of the native distal esophagus showed normal esophageal mucosa. In one patient, biopsy of the native distal esophagus showed a single glandular tube with signs of intestinal metaplasia. A target biopsy of a small mucosal elevation of the distal esophagus in another patient showed mild reactive changes of the mucosa. In two patients, biopsies of the stomach were obtained. Biopsies in one patient showed no abnormalities. In the other patient without macroscopic anomalies, biopsy of the stomach showed lymphoid infiltration, further investigation excluded lymphoma. None of the biopsies showed signs of esophageal dysplasia. In four patients without suspected macroscopic anomalies (36%), no biopsies specimens were taken.

Table 4 | Radiologic, endoscopic and histologic data

Variable	GPU (n=9)	JI (n=11)	p-value
Barium contrast results	*n=5*	*n=11*	
Stasis	3 (60%)	10 (91%)	-
Stricture	0	0	
Dilated JI graft **-Mild** **-Severe**	N/A	 4 (36%) 2 (18%)	N/A
Lengthening of JI graft	N/A	4 (36%)	N/A
Endoscopy results			
Length proximal esophagus (cm)	20 (17-24)	21 (18-25)	-
Length jejunal graft (cm)	N/A	15 (12-22)	-
Length distal esophagus (cm)	N/A	4.5 (0-8)	-
Macroscopic anomalies	5 (56%)	5 (45%)	1.0
Macroscopic esophagitis[a]			
-Grade A	0	1 (9%)	1.0
-Grade B	0	1 (9%)	1.0
Columnar lined esophagus	3 (33%)	0	0.03*
Histology results	*n=8*	*n=7*	
Normal mucosa	1(11%)	3 (27%)	0.58
Inflammation	2 (22%)	1 (9%)	1.0
Intestinal metaplasia	2 (22%)	0	0.47
Other	3 (33%)	3 (27%)	1.0
No biopsy specimen	1(11%)	4 (36%)	0.12

[a]According to the Los Angeles classification

**Indicating statistical significance*

Data are presented as median (range) or n (%)

Symptom and Graft analysis

Columnar lined esophagus of the native esophagus occurred significantly more often in the GPU group compared to the JI-group (p=0.03). No associations were found in GPU patients between reflux symptoms and macroscopic mucosal abnormalities during upper endoscopy or with intestinal metaplasia. Both patients that had confirmed intestinal metaplasia, reported reflux symptoms and were treated with PPIs. No association was found between intestinal metaplasia and GER symptoms. No association was found between BMI and reflux.
Of the six patients with a dilated JI-graft, five (83%) reported dysphagia complaints. Of the four patients with lengthening of the JI-graft, three reported dysphagia symptoms. However, there was no statistically significant association between dilatation or lengthening and dysphagia.

DISCUSSION

This is the first study to evaluate very long-term changes in ER grafts for LGEA by contrast study and endoscopy, showing intestinal metaplasia in 22% of GPU patients and graft dilatation in JI patients. Furthermore, this study evaluates gastrointestinal symptoms during a long-term follow-up.

We found that the majority of GPU patients had reflux symptoms, which is in line with the outcome of the study of Hannon et al[21]. In our study, reflux symptoms were assessed at the outpatient clinic by a gastroenterologist. EA patients might consider reflux symptoms as normal after prolonged periods of reflux. Symptom-related questions asked by a specialist may identify patients with reflux symptoms who would otherwise consider themselves free of symptoms[29]. This can explain the high incidence of reflux found in this study.

This study showed that reflux symptoms occurred less in JI patients compared to GPU patients. This difference may be explained by the fact that several physiological anti-reflux mechanisms are altered in GPU patients, such as the intrathoracic position of the stomach with a negative intrathoracic pressure and loss of the His angle[17]. In the JI patient group, the distal esophagus remained intact with an intra-abdominal position in all but one patient. Although peristalsis of the graft is not as efficient as a native esophagus, the other antireflux barriers are preserved.

Postoperative dysphagia was present in the majority of JI patients. Their nutritional status, however, was good on the long term and all JI patients had a full oral intake. This is in contrast to previous studies[30,31], with only 33-57% of JI patients tolerating a complete oral intake. This difference may be explained by the occurrence of severe postoperative complications in both studies, including graft loss.

In our study, GPU patients reported less dysphagia symptoms compared to JI patients. Our GPU group also reported less dysphagia symptoms than the GPU group of Hannon et al.[21], although this difference is relatively small.

Lower BMI has been described in GPU patients compared to primary repair EA patients[21]. This is in line with our findings, in which one third of the GPU patients were underweight and needed nutritional supplements. One might speculate that reflux negatively influences the achievement of an adequate caloric intake and consequent lower BMI[32,33]. However, in our study, an association between reflux and BMI could not be found.

Our study showed that the majority of patients had a dilated JI graft. Although almost all of these patients reported dysphagia complaints, an association between the dilatation and dysphagia was not statistically significant. Previously, JI graft dilatation has only been described by Saeki et al. in 1988[22]. In his study on JI for LGEA (mean age 10 years) dilatation of a graft was observed in one patient. This was due to a stenosis of the distal anastomosis. In our study, lengthening of the jejunal graft was seen in 36% of JI patients, which is in line with previous studies[22,23].

Upper endoscopy showed columnar lined esophagus in one third of the GPU patients and in none of the JI patients in our study. Histology reported intestinal metaplasia in 22% of GPU patients and in none of the JI patient. These findings are in contrast to the only other published study using endoscopy in adults after LGEA by Vergouwe et al.[34] The latter showed no signs of Barrett's esophagus in LGEA patients with ER. However, they showed an incidence of 6.6% Barrett's esophagus in their total cohort of 151 adult EA patients. Vergouwe et al.[20] also showed two patients with esophageal cancer. Esophageal cancer after primary repair of EA at the site of the anastomosis in a patient with severe reflux has also been described[34]. In our study, no patients were found with esophageal cancer.

Our findings reveal that the macroscopic and microscopic tissue changes seen in the GPU grafts were not significantly associated with reflux symptoms. This may be explained by the fact that many patients were treated with PPIs. Also, metaplasia of the esophageal mucosa can protect against acid reflux and therefore prevent symptoms of discomfort[42]. Furthermore, one can expect that EA patients may get used to reflux symptoms, although this is not evidence based. Reflux symptoms can thus not be used as a reliable detector for the presence of intestinal metaplasia. Since GPU is the most frequently performed ER procedure for LGEA and intestinal metaplasia or Barrett's esophagus may occur more frequently in this subset of patients, further follow-up of GPU in the long-term may clarify this concern. Barrett's esophagus in the normal population increases steeply from young adulthood until the 6th decade of life[35,36]. Since our cohort consists of young patients, the prevalence of Barrett's esophagus will become more clear after long term follow up .

Due to the rarity of LGEA, data are scarce. This inevitably limits our study and therefore, interpretations must be made with caution. Other limitations in this study include the retrospective design of the study and the missing histology in five JI patients and one GPU patient. Although the macroscopic aspects during endoscopy seemed normal in these patients, histological evidence would be preferred. Also, contrast studies were missing in four GPU patients. Furthermore, review of contrast studies is not standardized and therefore subjective. However, all contrast studies were analyzed by an experienced radiologist and pediatric surgeon to minimize bias.

CONCLUSION

This study shows that ER grafts show significant macroscopic and microscopic abnormalities after long-term follow-up. Dilatation of the graft and dysphagia symptoms were present in the majority of JI patients. GPU patients may have an increased risk of intestinal metaplasia. Therefore, increased awareness and follow-up is suggested for LGEA patients after ER. Especially since GPU has been and still is the most frequently used treatment for LGEA.

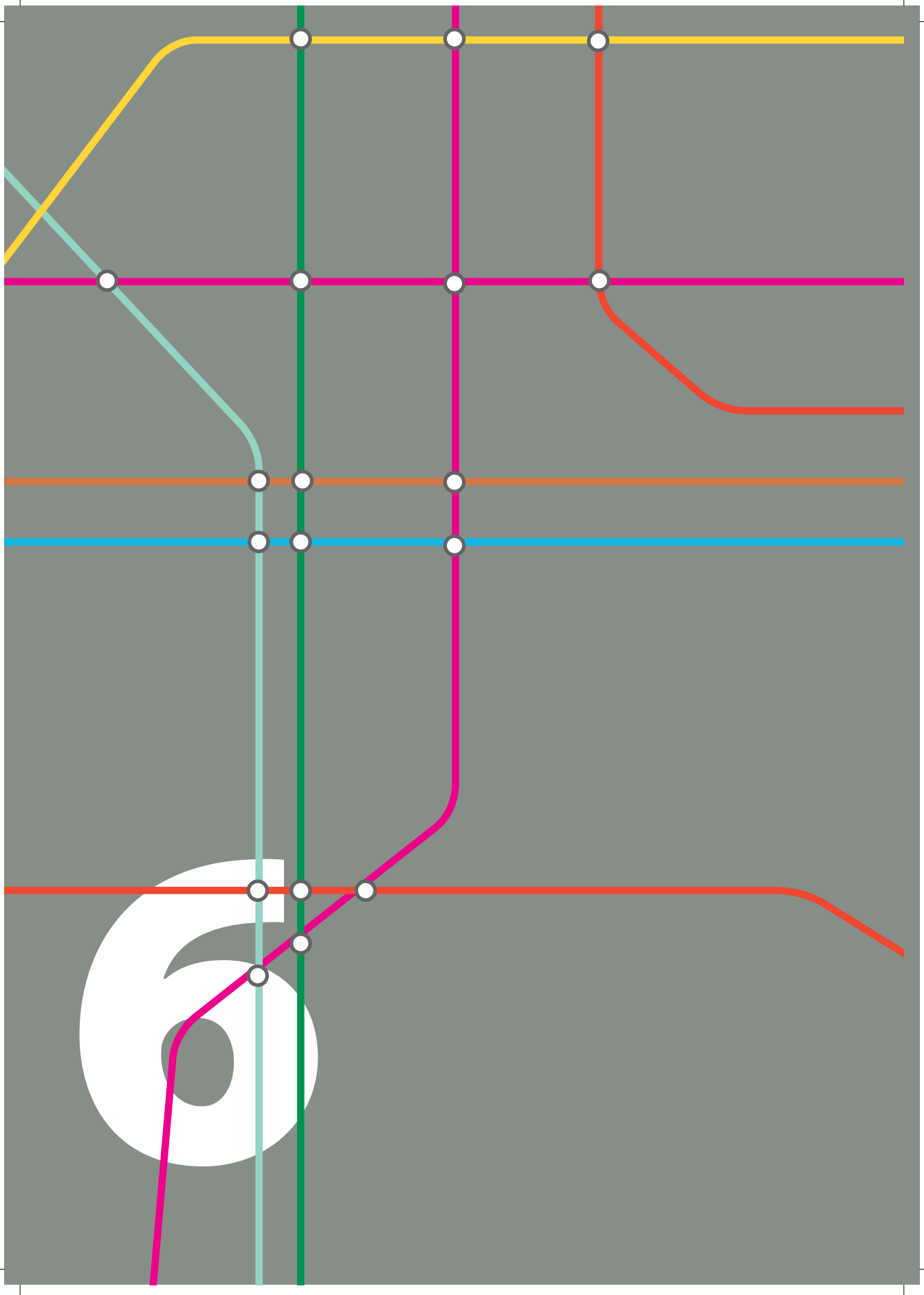
586319-L-bw-Gallo
Processed on: 28-11-2022

REFERENCES

1 Sfeir R, Michaud L, Salleron J, Gottrand F. Epidemiology of esophageal atresia. Dis Esophagus 2013; 26: 354–355. [DOI: 10.1111/dote.12051]
2 Holland AJA, Ron O, Pierro A, Drake D, Curry JI, Kiely EM, Spitz L. Surgical outcomes of esophageal atresia without fistula for 24 years at a single institution. J Pediatr Surg 2009; 44: 1928–1932. [PMID: 19853749 DOI: 10.1016/j.jpedsurg.2009.02.008]
3 Ron O, De Coppi P. The surgical approach to esophageal atresia repair and the management of long-gap atresia: results of a survey. Semin Pediatr Surg 2009; 18: 44–49. [DOI: 10.1053/J.SEMPEDSURG.2008.10.009]
4 Puri P, Ninan GK, Blake NS, Fitzgerald RJ, Guiney EJ, O'Donnell B. Delayed primary anastomosis for esophageal atresia: 18 Months' to 11 years' follow-up. J Pediatr Surg 1992; 27: 1127–1130. [DOI: 10.1016/0022-3468(92)90573-P]
5 Puri P, Khurana S. Delayed primary esophageal anastomosis for pure esophageal atresia. Semin Pediatr Surg 1998; 7: 126–129. [DOI: 10.1016/S1055-8586(98)70027-7]
6 van der Zee DC, Vieirra-Travassos D, Kramer WLM, Tytgat SHAJ. Thoracoscopic elongation of the esophagus in long-gap esophageal atresia. J Pediatr Surg 2007; 42: 1785–1788. [DOI: 10.1016/j.jpedsurg.2007.06.023]
7 van der Zee DC, Gallo G, Tytgat SHA. Thoracoscopic traction technique in long-gap esophageal atresia: entering a new era. Surg Endosc 2015; 29: 3324–3330. [DOI: 10.1007/s00464-015-4091-3]
8 Bogusz B, Patkowski D, Gerus S, Rasiewicz M, Górecki W. Staged Thoracoscopic Repair of Long-Gap Esophageal Atresia Without Temporary Gastrostomy. J Laparoendosc Adv Surg Tech 2018; 28: 1510–1512. [DOI: 10.1089/lap.2018.0188]
9 Foker JE, Linden BC, Boyle EM, Marquardt C. Development of a True Primary Repair for the Full Spectrum of Esophageal Atresia. Lippincott-Raven Publishers
10 Kimura K, Soper RT. Multistaged extrathoracic esophageal elongation for long-gap esophageal atresia. J Pediatr Surg 1994; 29: 566–568. [PMID: 8014818 DOI: 10.1016/0022-3468(94)90094-9]
11 Spitz L. Gastric transposition for esophageal substitution in children. J Pediatr Surg 1992; 27: 252–259. [DOI: 10.1016/0022-3468(92)90322-X]
12 Bax NMA, van der Zee DC. Jejunal pedicle grafts for reconstruction of the esophagus in children. J Pediatr Surg 2007; 42: 363–369. [DOI: 10.1016/J.JPEDSURG.2006.10.009]
13 Sherman CD, Waterston D. Oesophageal reconstruction in children using intrathoracic colon. Arch Dis Child 1957; 32: 11–6. [PMID: 13403705 DOI: 10.1136/adc.32.161.11]
14 Sulkowski JP, Cooper JN, Lopez JJ, Jadcherla Y, Cuenot A, Mattei P, Deans KJ, Minneci PC, Columbus P. Morbidity and mortality in patients with esophageal atresia. (e-pub ahead of print doi:10.1016/j.surg.2014.03.016).
15 Connor MJ, Springford LR, Kapetanakis V V., Giuliani S. Esophageal atresia and transitional care—step 1: a systematic review and meta-analysis of the literature to define the prevalence of chronic long-term problems. Am J Surg 2015; 209: 747–759. [DOI: 10.1016/J.AMJSURG.2014.09.019]
16 Gallo G, Zwaveling S, Van der Zee DC, Bax KN, de Langen ZJ, Hulscher JBF. A two-center comparative study of gastric pull-up and jejunal interposition for long-gap esophageal atresia. J Pediatr Surg 2015; 50: 535–539. [DOI: 10.1016/J.JPEDSURG.2014.05.026]
17 Orlando RC. Overview of the mechanisms of gastroesophageal reflux. Am J Med 2001; 111: 174–177. [PMID: 11749946 DOI: 10.1016/S0002-9343(01)00828-2]
18 Gallo G, Vrijlandt EJLE, Arets HGM, Koppelman GH, Van der Zee DC, Hulscher JBF, Zwaveling S. Respiratory function after esophageal replacement in children. J Pediatr Surg 2017; 52: 1736–1741. [DOI: 10.1016/J.JPEDSURG.2017.03.046]

19 Schachter LM, Dixon J, Pierce RJ, O'brien P. Severe Gastroesophageal Reflux Is Associated With Reduced Carbon Monoxide Diffusing Capacity*. DOI:10.1378/chest.123.6.1932
20 Vergouwe FWT, IJsselstijn H, Biermann K, Erler NS, Wijnen RMH, Bruno MJ, Spaander MCW. High Prevalence of Barrett's Esophagus and Esophageal Squamous Cell Carcinoma After Repair of Esophageal Atresia. Clin Gastroenterol Hepatol 2018; 16: 513-521.e6. [DOI: 10.1016/J.CGH.2017.11.008]
21 Hannon E, Eaton S, Curry JI, Kiely EM, Spitz L, De Coppi P. Outcomes in adulthood of gastric transposition for complex and long-gap esophageal atresia. J Pediatr Surg 2020; 55: 639–645. [PMID: 31519362 DOI: 10.1016/j.jpedsurg.2019.08.012]
22 Saeki M, Tsuchida Y, Ogata T, Nakano M, Akiyama H. Long-term results of jejunal replacement of the esophagus. J Pediatr Surg 1988; 23: 483–489. [PMID: 3379557 DOI: 10.1016/S0022-3468(88)80454-8]
23 Steves Ring W, Varco RL, L'Heureux PR, Foker JE. Esophageal replacement with jejunum in children. DOI:10.1016/s0022-5223(19)37190-9
24 Bax NMA, Rövekamp MH, Pull ter Gunne AJ, van der Zee DC. Early one-stage orthotopic jejunal pedicle-graft interposition in long-gap esophageal atresia. Pediatr Surg Int 1994; 9: 483–485. [DOI: 10.1007/BF00179446]
25 Bax KMA. Jejunum for bridging long-gap esophageal atresia. Semin Pediatr Surg 2009; 18: 34–39. [DOI: 10.1053/J.SEMPEDSURG.2008.10.007]
26 Spitz L. Oesophageal Atresia Treatment: A 21st-century Perspective. J Pediatr Gastroenterol Nutr 2011; 52: S12. [DOI: 10.1097/MPG.0b013e3182116082]
27 Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP, Johnson F, Hongo M, Richter JE, Spechler SJ, J Tytgat GN, Wallin L. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut 1999; 45: 172–180. [DOI: 10.1136/gut.45.2.172]
28 Sharma P, Dent J, Armstrong D, Bergman JJGHM, Gossner L, Hoshihara Y, Jankowski JA, Junghard O, Lundell L, Tytgat GNJ, Vieth M. The Development and Validation of an Endoscopic Grading System for Barrett's Esophagus: The Prague C & M Criteria. (e-pub ahead of print 2006; doi:10.1053/j.gastro.2006.08.032).
29 IJsselstijn H, van Beelen NWG, Wijnen RMH. Esophageal atresia: Long-term morbidities in adolescence and adulthood. Dis Esophagus 2013; 26: 417–421. [DOI: 10.1111/dote.12059]
30 Koivusalo A, Suominen J, Salminen J, Pakarinen M. Indications, Surgical Complications, and Long-Term Outcomes in Pediatric Esophageal Reconstructions with Pedicled Jejunal Interposition Graft. Eur J Pediatr Surg 2020; 30: 111–116. [DOI: 10.1055/s-0039-3402713]
31 Cauchi JA, Buick RG, Gornall P, Simms MH, Parikh DH. Oesophageal substitution with free and pedicled jejunum: short- and long-term outcomes. Pediatr Surg Int 2006; 23: 11–19. [DOI: 10.1007/s00383-006-1770-0]
32 Rosen R, Vandenplas Y, Singendonk M, Cabana M, Dilorenzo C, Gottrand F, Gupta S, Langendam M, Staiano A, Thapar N, Tipnis N, Tabbers M. Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutritio. J. Pediatr. Gastroenterol. Nutr. 2018. DOI:10.1097/MPG.0000000000001889
33 Baird DC, Harker DJ, Karmes AS. Diagnosis and treatment of gastroesophageal reflux in infants and children. Am Fam Physician (e-pub ahead of print 2015; doi:10.1016/S0002-838X(15)30303-8).
34 Pultrum BB, Bijleveld CM, De Langen ZJ, Plukker JTM. Development of an adenocarcinoma of the esophagus 22 years after primary repair of a congenital atresia. J Pediatr Surg (e-pub ahead of print 2005; doi:10.1016/j.jpedsurg.2005.08.042).

35 Rubenstein JH, Mattek N, Eisen G. Age- and sex-specific yield of Barrett's esophagus by endoscopy indication. Gastrointest Endosc. 2010 Jan;71(1):21-7. doi: 10.1016/j.gie.2009.06.035. Epub 2009 Sep 12.
36 Sfeir R, Michaud L, Salleron J, Gottrand F. Epidemiology of esophageal atresia. Dis Esophagus 2013; 26: 354–355. [DOI: 10.1111/dote.12051


6

CHAPTER 6

Quality of life after esophageal replacement in children

Gabriele Gallo, E.S. van Tuyll van Serooskerken, S.H.A.J. Tytgat, D.C. van der Zee, C.M.G. Keyzer-Dekker,S. Zwaveling, J.B.F. Hulscher, H. Groen, M.Y.A. Lindeboom

Journal of Pediatric Surgery 2021 Feb;56(2):239-244.

ABSTRACT

Purpose

Assessing quality of life (QoL) after esophageal replacement (ER) for long-gap esophageal atresia (LGEA).

Methods

All patients after ER for LGEA with gastric pull-up (GPU n=9) or jejunum interposition (JI n=14) in University Medical Center Groningen and Utrecht (1985-2007) were included. QoL was assessed with 1) gastrointestinal-related QoL using the Gastrointestinal Quality of Life Index (GIQLI), 2) general QoL (Child Health questionnaire CHF87-BREF (children)/World Health Organization questionnaire WHOQOL-BREF (adults)), and 3) health-related QoL (HRQoL) (TNO AZL TACQoL / TAAQoL). Association of morbidity (heartburn, dysphagia, dyspnea on exertion, recurrent cough) and (HR)QoL was evaluated.

Results

Six patients after GPU (75%) and eight patients after JI (57%) responded to the questionnaires (mean age 15.7, SD 5.9, 12 male, two female). Mean gastrointestinal, general and health-related QoL total scores of the patients were comparable to healthy controls. However young adults reported a worse physical functioning (p=0.02) but better social functioning compared to peers (p=0.01). Morbidity was not associated with significant differences in (HR)QoL.

Conclusions

With the current validated QoL most patients after ER with GPU and JI for LGEA have normal generic en disease specific QoL scores. Postoperative morbidity does not seem to influence (HR) QoL.

INTRODUCTION

Esophageal atresia (EA) is a rare congenital disorder characterized by absence of esophageal continuity. In most patients, a primary anastomosis can be performed. However, if the distance between the two esophageal remnants is too wide for primary repair, esophageal replacement (ER) strategies may have to be deployed. Replacement with jejunum[1-3], colon[4], or stomach[5] have all been advocated.

Gastrointestinal and respiratory morbidity have been investigated after primary anastomosis for EA[6-11]. Long term morbidity after primary EA repair has considered to be moderate and QoL in adults patients has demonstrated to be excellent[12-13]. However long-term morbidity for long-gap esophageal atresia (LGEA) appears to be significant. Only a few studies have investigated QoL after ER and mostly without using validated tools. QoL after jejunum interposition has never been analyzed before. We hypothesized that the long term QoL will be diminished in patients who underwent ER in comparison to healthy controls. For optimal care of children after ER and their transition from pediatric to adult healthcare, we should have knowledge of their medical, as well as psycho-social status. Therefore, this study aims to investigate QoL after ER for LGEA in children and young adults and analyze whether morbidity might influence patients' well-being.

PATIENTS AND METHODS

A cross-sectional cohort study was performed. All patients that had undergone a gastric pull-up (GPU) at the University Medical Center Groningen (UMCG) between 1985-2006 and jejunal interposition (JI) at the University Medical Center Utrecht (UMCU) between 1988-2007 for LGEA were included. At the time of the study GPU was the preferred method in the UMCG and a JI was the preferred method in the UMCU. In this cohort, patient were diagnosed with a LGEA if a primary end-to-end anastomosis was not feasible due to the distance between the proximal and distal esophagus measured under fluoroscopy.
Primary endpoint of the present study was the assessment of HRQoL and QoL outcome in LGEA patients after JI or GPU.
Secondary endpoint was the evaluation of morbidity parameters associated with (HR)QoL.

Ethical Approval

This assessment was conducted in accordance with the local medical ethics review boards of the University Medical Center Groningen (UMCG, Ref. M14.159735) and University Medical Center Utrecht (UMCU, Ref. WAG/om/15/001186).

MEASUREMENTS

Patient characteristics were collected from the medical records. Sociodemographic aspects were assessed using structured questions on marital status; education and occupation.

Quality of Life measurements

QoL was assessed using validated questionnaires. The QoL measures were self-report measurements. Three areas were investigated: Disease-Specific QoL using the Gastrointestinal Quality of Life Index (GIQLI), general QoL using the CHF87-BREF (children) and WHOQOL-BREF questionnaire (adults), and health-related QoL using the TACQoL (children 6-15 years old) and TAAQoL (patients aged 16 years and older).

Disease-Specific QoL

The GIQLI, introduced by Eypasch et al.[15], is a validated tool to assess HRQoL in patients with gastrointestinal (GI) disease and especially in those who underwent surgery. The questionnaire contains 36 items, each with five response categories concerning gastrointestinal disease-related symptoms, physical status, emotions and psychosocial functions. The questionnaire is developed with 5-point Likert scale, ranging from 0 to 4, with 4 implying the least complaints (a higher score represents a better QoL). The theoretical maximum score is 144 points. A GIQLI score less than 105 indicates that the responder experiences persistent GI symptoms[14]. Patients with a total score of less than 105 were therefore considered as symptomatic.

General QoL

The Child Health Questionnaire Child Form (CHQ-CF87)16 measures psychosocial and physical well-being in patients of 5 to 18 years of age. It provides a qualitative assessment of overall health status across multiple domains. It consists of 87 items divided into 10 multi-item scales, per scale items are summed up and transformed into a 0 (worst possible score) to 100 (best possible score) scale.

The WHOQOL-BREF[17] is a QoL assessment developed by the WHOQOL group for adults. It consists of 26 items in four different domains and a general QoL facet. The domains are physical health, psychological health, social relationships, and family/social environment. The response scales are 5-point Likert scales. A higher score represents a better QoL.

Health-related QoL

HRQoL is a combination of health problems and emotional responses towards these health problems. It reflects the subjective perception of health and is increasingly recognized as a relevant 'patient-reported outcome' since it measures the emotional impact of self-reported functional problems[18-19].

HRQoL was assessed using TACQOL/TAAQOL20-23 questionnaires developed by The Netherlands Organization (TNO) for Applied Scientific Research and the Academic Hospital in Leiden (LUMC),

which explicitly offers respondents the possibility to differentiate between their functioning and the way they feel about it.

The TACQOL (for children 6-15 years old) contains 7 domains: social functioning, autonomous functioning, physical complaints, motoric functioning, cognitive functioning, positive emotions and negative emotions.

The TAAQOL (for patients aged 16 years and older) consists of 12 domains: gross motor functioning, fine motor functioning, cognition, sleep, pain, social contacts, daily activities, sex, vitality, happiness, depressive mood and anger. Items are scored on a 0–4 point Likert scale. Scales are transformed to a 0–100 scale, with higher scores representing a better HRQoL.

Parameters of morbidity and QoL

Relation between (HR)QoL measurements and post-operative symptoms such as heartburn, dysphagia, dyspnea on exertion, recurrent pneumonia and cough and post-operative surgical re-intervention (anastomotic revision and esophageal dilatations) were investigated.

STATISTICAL ANALYSIS

Data were entered into a SPSS database and statistical analysis was performed using SPSS (SPSS version 23 9SPSS Inc., Chicago, IL). Data were expressed as mean ± SD Continuous variables, group differences were analyzed using one sample t-test, and two sample t-test for CHQ. To examine differences in (HR)QoL between GPU and JI, the means of the two groups were compared using two sample t-tests. Because children completed either the TACQOL or the TAAQOL, depending on age, age-appropriate z-scores of the two were compared. (HR)QoL measurements of patients reporting a specific complain at last follow-up (e.g. heartburn) were compared with those of patients not presenting that symptom using Mann-Whitney U test. Statistical differences were considered as significant for p-value < 0.05.

RESULTS

In total nine GPU and 14 JI patients had undergone an ER for LGEA at the UMCG and UMCU respectively. Six of the GPU and eight JI patients had responded to the questionnaires and could be evaluated for this study. Mean age of the 14 responders was 15.7 +/-5.9 SD (12male, two female).

No differences were found in patient characteristics between responders and non-responders (Table 1a). Characteristics of patients joining the study are shown in Table 1b. Sociodemographic factors did not differ in the two groups (see Table 2). The median follow-up duration after surgery was 12 years (4-24): 12 years (4-17) after GPU and 14 years (7-24) after JI (Table 8).

Table 1a | Responders vs Non-responders patients characteristics. GPU (gastric pull-up), JI (jejunum interposition)

	Responders ***(n=14)***	**Non-responders** ***(n=9)***	***P value***
Gestational age ***(weeks)***	35.2 *(+/-2.9)*	34.4 *(+/-3.2)*	0.5
Weight at birth ***(gr)***	2150 *(+/-755)*	2154 (+/-740)	0.8
Type atresia A	5	1	0.3
Type atresia B	8	7	0.4
Type atresia C	1	1	1
Age at surgery ***(days)***	124 (+/-104)	100 (+/-89)	0.4
Any VACTERL anomalies	8 *(57%)*	5*(55%)*	1
Cardiac			
Renal	4	2	1
Anorectal	2	3	0.3
Vertebral	2	1	1
	3	3	1
GPU	6 *(21%)*	3 *(33%)*	1
JI	8 *(57%)*	6 *(66%)*	1

Table 1b | Patient characteristics

	Total *(n=14)*	**GPU *(n=6)***	**JI *(n=8)***	***P value***
Gestational age *(weeks)*	35.2 *(+/-2.9)*	34.6 (+/-3.6)	35.6 (+/-2.5)	0.6
Weight at birth *(gr)*	2150 *(+/-755)*	2054 (+/-685)	2221 (+/-842)	0.8
Type atresia A	5	4	1	0.09
Type atresia B	8	1	7	0.02
Type atresia C	1	1	0	0.4
Gastrostomy	14	6 (100%)	8 (100%)	1
Age at surgery *(days)*	124 (+/-104)	140.5 (+/-90)	111.8 (+/-118)	0.3
Any VACTERL anomalies	8 (57%)	5(83%)	3(37%)	0.1
Cardiac	4	2	2	1
Renal	2	2	0	0.1
Anorectal	2	1	1	1
Vertebral	3	3	0	0.05
Anastomotic leak requiring re-intervention	3 (21%)	0	3 (37.5%)	0.2

Table 2 | Sociodemographic factors.

	Total *(n=14)*	**GPU *(n=6)***	**JI *(n=8)***	***P value***
Mean age	15.7 +/-5.9 (6-28)	17.7 +/- 5.5 (8-28)	14.3 +/- 6.2 (6-25)	0.4
Still student	43% (6)	33% (2)	50% (4)	0.6
Ever flunked	50% (7)	66.7% (4)	37.5% (3)	0.5
Additional job	21.4% (3)	33% (2)	12.5% (1)	0.5
Finished with studies and unemployed	- (0)	- (0)	- (0)	-
Currently full time job	14.3% (2)	16.7% (1)	12.5% (1)	1
Partner	7% (1)	- (0)	12.5% (1)	1
Living alone	28.6% (4)	16.7% (1)	37.5% (3)	0.5
Living with partner	- (0)	- (0)	- (0)	-
Living with parents	71.4% (10)	83.3% (5)	62.5% (3)	0.5
Having children	- (0)	- (0)	- (0)	-

Table 8 | Postoperative morbidity.

Gastrointestinal QoL (GIQLI)

There was no significant differences between the total mean score of both patients groups (n14) (124.2, SD 11.0 vs) 125.8, SD 13.0, p=0.6) and healthy controls. One JI patient reported a total score of less than 105 and was considered symptomatic (Table 3). No significant differences were found between the different domains of the GIQLI.

Table 3 | Disease specific QoL evaluated using GIQLI

	GPU *(n=6)*		**JI *(n=8)***		
	Mean	**SD**	**Mean**	**SD**	***P value***
Physical well being	23	5.1	23.5	3.5	*0.9*
Gastrointestinal symptoms	65.8	4	63.1	8.7	*0.8*
Social well being	19.3	1	18.7	17.3	*0.3*
Emotional well being	18	1.6	17.4	1.9	*0.4*
Total	126.1	10.9	122.7	13.1	*0.6*

Generic QoL

There was no significant differences between the total mean score of the children after ER and healthy controls (Table 4). Three children after ER (21%), had a very low mean score (<-2SD) in the domains pain, general behavior and emotional functioning.

There was no significant differences between the total mean score of the young adults after ER and healthy controls. In the domain physical functioning young adults scored significantly lower compared to healthy controls (16.9 (SD 1.5) vs 18.3 (SD 3), p=0.02). In the domain environment, mean scores were higher than in healthy controls (17.2 (SD 1.7) vs 15.9 (SD 2.8), p=0.05). None of the young adults scored below -2SD (Table 5). No statistically significant differences were found between GPU and JI in QoL measurements, the mean z-score of QoL after GPU was 0.0015 (SD 0.9) and after JI was 0.09 (SD 0.7), p=0.6

Table 4 | QoL evaluated using CHQ

	Patients *(n=7)*		**Controls**		
	Mean	**SD**	**Mean**	**SD**	***P value***
Physical functioning	97.3	3.5	96.8	5.4	0.7
Role functioning-emotional	90.4	20.7	92.3	16.8	0.8
Pain	75.7	26.9	78.2	19.5	0.8
General behaviour	82.1	16.5	83.6	10.2	0.8
Self esteem	76.7	5.2	75.4	12.5	0.5
General health	65.2	11.7	74.6	15.9	0.07
Mental health	84.3	8.6	78.2	13	0.1
Family cohesion	86.4	18	75.7	23.1	0.1

Table 5 | QoL evaluated using WHOQoL

	Patients *(n=9)*		**Controls**		
	Mean	**SD**	**Mean**	**SD**	***P value***
Physical functioning	16.9	1.5	18.3	3	*0.02*
Psychological functioning	16.3	1.6	16.1	2.8	*0.6*
Social Relationship	16.5	2.2	15.8	3.3	*0.3*
Environment	17.2	1.7	15.9	2.8	*0.05*

HRQoL

Children after ER scored significantly higher than healthy controls in both the positive (15.6 (SD 0.5) vs 13.0 (SD 2.8), p=0.00) and negative (13.6 (SD 1.6) vs controls 11.6 (SD 2.5), p=0.01) emotion domains. One child after JI scored <-2SD in the domain autonomy. In the other domains no differences were found (Table 6).

In the domain social functioning, young adults scored significantly better than the controls (95.8 (SD 7.5) vs 83.7 (19.2 SD) p=0.01). More aggressive emotions (98.1, SD 4.5) were reported by young adults compared with healthy controls (87.6, SD 16.8, p=0.002). In the other domains no differences were found. One young adult after JI scored <-2SD in the domain sleep (Table 7). No statistically significant differences were found between GPU and JI in HRQoL measurements, the mean z-score of HRQoL after GPU was 0.409 (SD 0.62) and after JI was 0.171 (SD 0.82), p=0.077

Table 6 | HRQoL evaluated using TACQOL

	Patients *(n=9)*		**Controls**		
	Mean	**SD**	**Mean**	**SD**	***P value***
Physical functioning	26.0	3.2	23.6	5.3	*0.07*
Motor functioning	29.6	2.6	29.7	3.2	*0.9*
Congitive functioning	27.2	3.5	27.5	4.1	*0.8*
Autonomy	30.7	3.5	31.0	2.9	*0.8*
Positive moods	15.6	0.5	13.0	2.8	*0.00*
Negative moods	13.6	1.6	11.6	2.5	*0.01*

Table 7 | HRQoL evaluated using TAAQOL

	Patients *(n=7)*		**Controls**		
	Mean	**SD**	**Mean**	**SD**	***P value***
Cognitive functioning	89.5	10.2	82.7	22.8	*0.1*
Sleep	67.7	21.8	73.8	26.1	*0.5*
Pain	82.2	18.7	73.2	24.2	*0.2*
Social functioning	95.8	7.5	83.7	19.2	*0.01*
Daily activities	86.4	20.3	83.4	24.8	*0.7*
Sexuality	87.5	13.6	84.4	25.7	*0.6*
Vitality	54.1	18	63.8	23.9	*0.2*
Positive emotions	76.3	14.3	64.5	21.8	*0.8*
Depressive emotions	81.9	13.3	77.9	20.6	*0.4*
Aggressive emotions	98.1	4.5	87.6	16.8	*0.002*

Parameters associated with QOL

Re-intervention due to anastomotic leakage and esophageal dilatations were not associated in a change in (HR)QoL. Post-operative symptoms were not associated with significant differences in (HR)QoL measurements (Table 9a, 9b, 10).

Table 8 | Postoperative morbidity.

	GPU (n=6)	JI (n=8)	TOTAL (n=14)
Heartburn	1 *(16%)*	1 *(12%)*	2 *(14%)*
Esophageal dilatation	3 *(50%)*	1 *(12%)*	4 *(28%)*
Episodic dysphagia	3 *(50%)*	4 *(50%)*	7 *(50%)*
Asthma-like symptoms	2 *(33%)*	0 *(-)*	2 *(14%)*
Recurrent pneumonia	1 *(15%)*	2 *(25%)*	3 *(21%)*
Dyspnea on exertion	3 *(50%)*	2 *(25%)*	5 *(35%)*
Recurrent cough	2 *(33%)*	3 *(37%)*	5 *(14%)*
Re-operation	0 *(-)*	3 *(37%)*	3 *(21%)*

Table 9a | Relation between morbidity and HRQoL measurements in patients up to 15 years old (TACQoL). Data are reported as p value. A p value < 0.05 indicates a symptom associated with significant lower HRQoL measurement.

	Physical function	Motor function	Cognitive function	Autonomy	Positive moods	Negative moods
Heartburn	1	0.5	0.8	0.5	0.8	0.3
Esophageal dilatation	1	0.6	0.4	0.2	0.6	0.7
Dysphagia	0.5	0.1	0.7	0.3	0.6	0.1
Asthma-like symptoms	0.4	0.5	0.7	0.6	0.3	0.1
Recurrent pneumonia	1	0.5	0.8	0.5	0.8	0.3
Dyspnea on exertion	0.4	0.2	0.7	0.6	0.3	0.4
Recurrent cough	1	0.4	0.1	0.2	0.6	0.2
Re-operation	0.1	0.09	0.4	0.6	0.2	0.7

Table 9b | Relation between HRQoL measurements in patients aged 16 years and older (TAAQoL) and morbidity. Data are reported as p value. A p value < 0.05 indicates a symptom associated with significant lower HRQoL measurement.

	Heartburn	Esophageal dilatation	Episodic dysphagia	Asthma-like symptoms	Recurrent pneumonia	Dyspnea on exertion	Recurrent cough	Re-operation
Cognitive functioning	0.1	0.3	0.6	0.8	0.2	0.6	0.1	0.2
Sleep	0.1	0.5	1	0.6	0.4	0.2	0.1	0.4
Pain	0.2	1	0.8	0.4	1	0.6	0.2	0.2
Social functioning	0.4	0.7	0.2	0.4	0.4	0.2	0.4	0.2
Daily activities	0.3	0.8	0.6	0.1	0.6	0.1	0.3	0.6
Sexuality	0.3	0.4	1	0.1	1	0.1	0.3	1
Vitality	0.3	0.2	1	0.6	0.2	0.4	0.3	0.2
Positive emotions	1	1	0.4	0.4	0.4	0.4	1	0.2
Depressive emotions	1	0.3	0.3	1	0.4	0.8	1	0.5
Aggressive emotions	0.6	0.3	0.4	0.1	0.1	0.4	0.6	0.4

Table 10 | Relation between morbidity and QoL measurements (WHOQoL). Data are reported as p value. *A p value < 0.05 indicates a symptom associated with significant lower QoL measurement.*

	Physical function	Psychological function	Social relations	Environment
Heartburn	0.8	0.4	0.2	0.8
Esophageal dilatation	0.2	0.4	0.1	0.1
Dysphagia	0.3	1	0.1	0.9
Asthma-like symptoms	0.3	0.1	0.6	0.6
Recurrent pneumonia	0.8	1	1	0.7
Dyspnea on exertion	0.6	1	0.6	0.7
Recurrent cough	0.8	0.4	0.2	0.8
Re-operation	0.8	0.5	0.1	0.5

DISCUSSION

This study investigated (HR)QoL in children and young adults after ER for LGEA. It is the first study on (HR)QoL after JI in children and young adults. We found that generic and disease specific QoL in the majority of patients after ER is comparable to normal QoL scores as measured in healthy population. No significant differences in (HR)QoL were found between GPU and JI patients. Furthermore, postoperative morbidity is not associated with changes into (HR)QoL.

In this study we found gastrointestinal-related QoL (GIQLI) to be generally good: only one patient (JI) scored below the cut-off for symptomatic patients, no significant differences were found between the groups and the controls, nor between the two groups. Recently Hannon et al. analyzed gastrointestinal-related QoL using GIQLI in 32 patients after GPU. Eighteen of them had a GPU for LGEA while in fourteen patients GPU was performed as rescue procedure after failed primary repair or colon interposition[26]. Results showed that the median gastrointestinal-related QoL according to GIQLI was 113, therefore above the cut-off point of symptomatic impairment (105), comparable to our findings. Dingemann et al. investigated gastrointestinal-related QoL in 27 patients who had an ER for complex/complicated esophageal atresia. GIQLI scores were found significantly worse when compared to the reference group[25]. A recent systematic review 14 reported significant worse GIQLI measurements for LGEA patients compared to the norm population, however the majority of patients included underwent colon interposition as ER procedure. These results appear to be in contrast with our findings, however differences in the surgical strategies make comparison complicated.

In our study general QoL in children after ER appeared comparable to the healthy population. There was no difference in the general QoL in young adults compared to healthy controls. However, young adults scored significantly worse on the domain physical functioning. Despite the physical limitation, the general QoL seems normal in young adults.

HRQoL was comparable to population average for both children and young adults. Young adults perceive their social functioning better than controls but described more aggressive emotions compared to the population average. This appears to be in contrast with previous studies investigating social functioning of children with chronic illness[27-28], and it might reflect a shift in the coping mechanisms of patients after ER towards a higher emotional sensitivity. Dingemann et al.[25] analyzed also HRQoL (KIDSCREEN27). Conform to our findings HRQoL was perceived as generally good and with regard to the domain physical well-being patients scored even better than controls. However, a correlation between long-term morbidity and HRQoL was not investigated in this series. We did not identify significant differences in (HR)QoL after the two surgical procedures. Patients after GPU reported HRQOL measurements higher than JI patients although not statistically significant ($p = 0.077$).

In this study the relationship between postoperative morbidity and (HR)QoL was analyzed. gastrointestinal and respiratory parameters were not associated with significant differences in (HR)QoL measurements. This outcome might suggest that physical complaints in ER patients do not affect patients' perception of well-being. This may be due to the fact that LGEA patients and their families have accepted this morbidity. Patients and their families might have developed efficient coping strategies in order to face the challenges of life after ER. Interestingly, it has been suggested that patients with congenital diseases might report even better QoL scores than children with acquired conditions, due to stronger coping strategies elaborated from early childhood[30-31]. Fifty-seven patients that had a primary correction of EA demonstrated indeed better QoL measurements compared to children with diabetes and asthma[32].

Patients after ER might seek stability by evolving their expectations and conceptions of themselves and their social role[33]. LGEA patients might have developed different internal standards for daily activities compared to peers. They might have elaborated different life values and might have re-conceptualized their physical limitations, leading to paradoxical satisfactory findings when responding to the present questionnaires. Family influences on patient's daily life have to be considered as well. Parents of chronically ill children tend to overprotect their sick children[34]. One might assume that this happens for patients after ER as well. Although this is comprehensible parental behavior it might represent a limitation to develop children's social functioning during adolescence. Moreover, somatic morbidity may affect the development of their personal identity and consequently may lead to social marginalization during a time when self-esteem largely depends on the acceptancy by peers. Therefore, physicians should encourage the family of patients after ER to promote and sustain the social contacts and autonomy of their children. However, even if we noticed a shift towards more emotional sensitivity during transition into adulthood, emotional development seems adequate, with outcomes such as vitality, social and cognitive functioning comparable to controls.

Limitations of this study is the small sample size that may lead to the lack of significant differences between the two groups.

The GIQLI questionnaire represents a valid tool for evaluation of disease-specific QoL in patients with gastrointestinal disorder but it is not tailored for patients with esophageal atresia. Dellenmark-Blom et al.[35] recently developed and validated a German and Swedish condition-specific HRQoL tool for patients who had a primary correction of EA. When implementing this for children with LGEA and ER it might represent a more appropriate instrument to investigate disease-specific QoL in our patients. To date, however, this questionnaire has not yet been validated for the Dutch population.

CONCLUSION

With the current validated QoL questionnaires most patients after ER with GPU and JI for LGEA have normal generic en disease specific QoL scores. Postoperative morbidity and surgical reintervention do not seem to influence (HR)QoL. The question remains if non condition specific HRQoL tools are suitable for this specific patients group. Condition specific HROLQ tools may provide more detailed information on HRQoL for all EA patients. We expect that these tools may provide a tailor-made support if necessary.

Acknowledgements: we would like to express our gratitude to R. Stellato, Assistant Professor of biostatistics at the Julius Center (UMC Utrecht) who provided statistical support for the study

REFERENCES

1 Bax NMA, M. H. Riivekamp, A. J. Pull ter Gunne, and D. C. van der Zee. Early one-stage orthotopic jejunal pedicle-graft interposition in long-gap esophageal atresia. Pediatr Surg Int (1994) 9: 483-485

2 Bax NMA, van der Zee DC. Jejunal pedicle grafts for reconstruction of the esophagus in children. J Pediatr Surg 2007;42(2):363-369

3 Bax NMA. Jejunum for bridging long-gap esophageal atresia. Semin Pediatr Surg. 2009 Feb;18(1):34-9. doi: 10.1053/j.sempedsurg.2008.10.007

4 Hamza AF. Colonic replacement in cases of esophageal atresia. Semin Pediatr Surg 2009;18(1):40–43

5 Spitz L. Gastric transposition for esophageal substitution in children. J Pediatr Surg. 1992 Feb;27(2):252-7; discussion 257-9. Review.

6 Gallo G, Zwaveling S, Groen H, Van der Zee D, Hulscher J. Long-gap esophageal atresia: a meta-analysis of jejunal interposition, colon interposition, and gastric pull-up. Eur J Pediatr Surg 2012;22 (6):420–425

7 Gallo G, Zwaveling S, Van der Zee DC, Bax NMA, de Langen ZJ, Hulscher JBF. A two-center comparative study of gastric pull up and jejunal interposition for long-gap esophageal atresia. J Pediatr Surg. Epub 2014 Jul 11. doi: 10.1016/j.jpedsurg.2014.05.026

8 Gallo G, et al, Respiratory function after esophageal replacement in children, J Pediatr Surg (2017), http://dx.doi.org/ 10.1016/j.jpedsurg.2017.03.046

9 Jönsson L, Friberg LG, Gatzinsky V, Kötz K, Sillén U, Abrahamsson K. Treatment and Follow-Up of Patients with Long-Gap Esophageal Atresia: 15 Years' of Experience from the Western Region of Sweden. Eur J Pediatr Surg 2015 Jan 5. In press. doi: 10.1055/s-0034-1396415

10 Olbers J, Gatzinsky V, Jönsson L, Friberg LG, Abrahamsson K, Sillén U, Gustafsson P. Physiological Studies at 7 Years of Age in Children Born with Esophageal Atresia. Eur J Pediatr Surg. 2014. In press doi: 10.1055/s-0034-1390017

11 Sistonen S, Malmberg P, Malmström K, Haahtela T, Sarna S, Rintala RJ, Pakarinen MP. Repaired oesophageal atresia: respiratory morbidity and pulmonary function in adults. Eur Respir J. 2010 Nov;36(5):1106-12

12 Koivusalo A, Pakarinen MP, Turunen P, et al. Health-related quality of life in adult patients with esophageal atresia—a questionnaire study. J Pediatr Surg 2005;40: 307–12.

13 Deurloo JA, Ekkelkamp S, Hartman EE, et al. Quality of life in adult survivors of correction of esophageal atresia. Arch Surg 2005;140:976–80.

14 S.P. Tan Tanny, et al., Quality of life assessment in esophageal atresia patients: a systematic review focusing on long-gap esophageal. J Pediatr Surgery, Available online 5 October 2019, https://doi.org/10.1016/j.jpedsurg.2019.08.040

15 Eypasch E, Troidl H, Wood-Dauphinee S, et al. Quality of life and gastrointestinal surgery - a clinimetric approach to developing an instrument for its measurement. Theor Surg 1990;5:3– 10.

16 Raat H, Mangunkusumo RT, Landgraf JM, Kloek G, Brug J.Feasibility, reliability, and validity of adolescent health statusmeasurement by the Child Health Questionnaire Child Form(CHQ-CF): internet administration compared with the stan-dard paper version. Qual Life Res 2007; 16: 675–85.

17 The WHOQOL Group. Development of the World Health Organization WHOQOL-BREF quality of life assessment. Psychol Med 1998;28(3):551–558

18 Rajmil L, Perestelo-Perez L, Herdman M. Quality of life and rare diseases. Adv Exp Med Biol 2010;686:251-72.

19 Orr, J. G. et al. Health related quality of life in people with advanced chronic liver disease. J. Hepatol. 61, 1158–1165 (2014).

20 Vogels T, Verrips GH, Verloove-Vanhorick SP, Fekkes M, Kamphuis RP, Koopman HM, et al. Measuring health-related quality of life in children: the deve lopment of the TACQOL-Parent Form. Eur J Public Health 1998;9:188-93

21 Verrips GH, Vogels A, Verloove-Vanhorick SP, Fekkes M, Koopman HM, Kamphuis RP, et al. Health-related quality of life measure–the TACQOL. J Appl Ther 1997;1:357-60

22 Bruil J, Fekkes T, Vogels T, Verrips GHW. TAAQOL Manual. Leiden: Leiden Center for Child Health and Pediatrics LUMC-TNO; 2004.

23 Vogels T, Verrips GHW, Koopman HM, Theunissen NCM, Fekkes M, Kamphuis RP. TACQOL Manual: Parent form and child form. Leiden: Leiden Center for Child Health and Pediatrics LUMC-TNO; 2000.

24 Ludman L, Spitz L (2003) Quality of life after gastric transposition for oesophageal atresia. J Pediatr Surg 38(1):53–57

25 Dingemann C (2014) Long-term health-related quality of life after complex and/or complicated esophageal atresia in adults and children registered in a German patient support group. J Pediatr Surg. 2014 Apr;49(4):631-8

26 E. Hannon, S. Eaton, J.I. Curry, et al., Outcomes in Adulthood of Gastric Transposition for Complex and Long-Gap Esophageal Atresia, J Pediatr Surg, https://doi.org/10.1016/j.jpedsurg.2019.08.012

27 Meijer et al (2000) Social functioning in children with a chronic illness. J.Child Psychol.Psychiat.;41(3)309-317

28 Gartstein M, Noll R, Vannata K (2000) Childhood aggression and chronic illness: possible protective mechanisms. J Applied Developmental Pyschology:21(3):315-333

29 Gallo G, et al, Respiratory function after esophageal replacement in children, J Pediatr Surg (2017), http://dx.doi.org/ 10.1016/j.jpedsurg.2017.03.046

30 Ure BM, Slany E, Eypasch EP, et al. Quality of life more than 20 years after repair of esophageal atresia. J Pediatr Surg 1998;33:511–5.

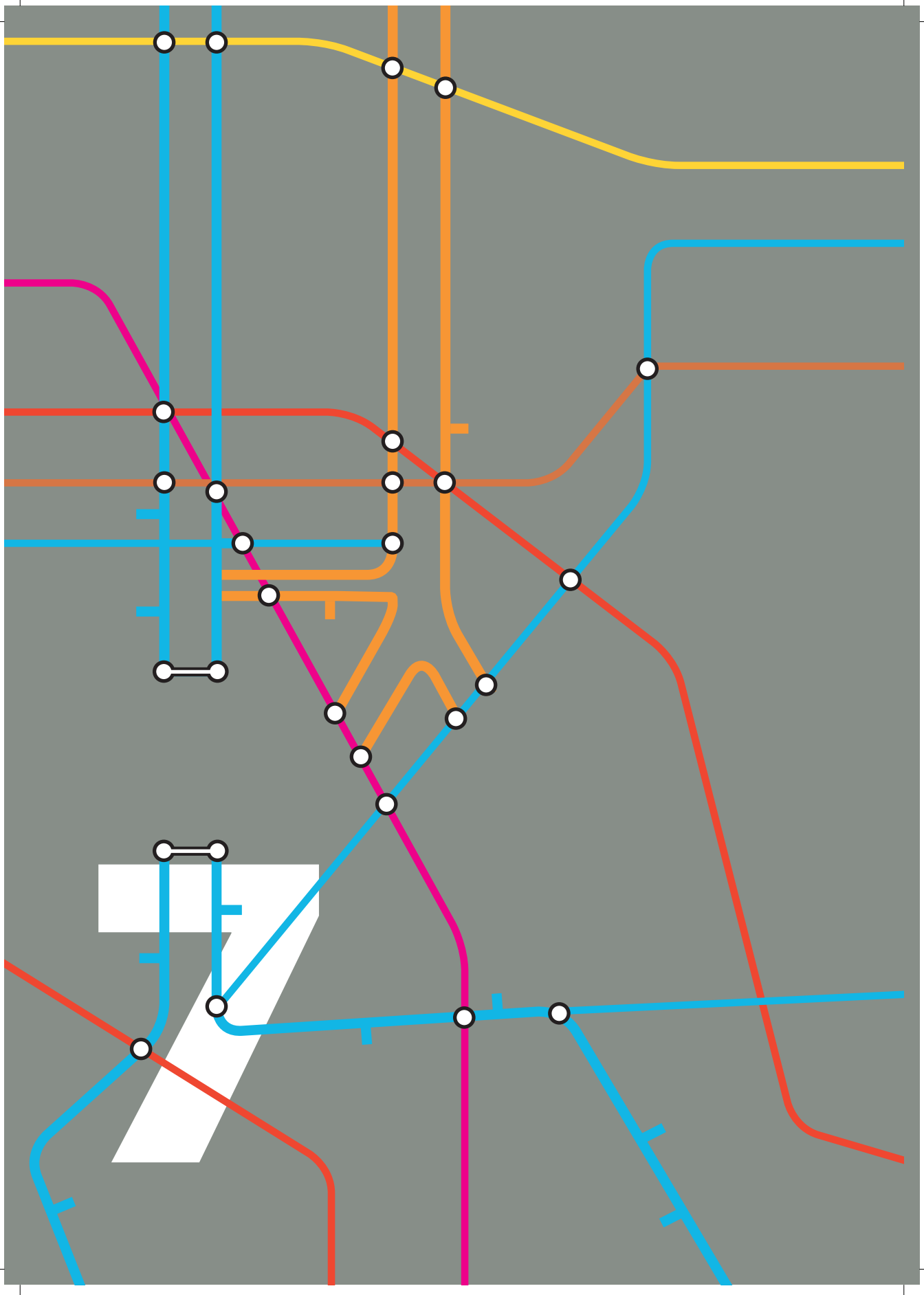
31 Deurloo JA, Ekkelkamp S, Bartelsman JF, et al. Gastroesophageal reflux: prevalence in adults older than 28 years after correction of esophageal atresia. Ann Surg 2003;238:686–9.

32 Legrand C, Michaud L, Salleron J, et al. Long-term outcome of children with oesophageal atresia type III. Arch Dis Child 2012;97:808–11.

33 Schwartz CE et al. Response shift theory: important implications for measuring quality of life in people with disability. Arch Phys Med Rehabil 2007;88:529-36.

34 Holmbeck GN, et al. Observed and perceived parental overprotection in relation to psychosocial adjustment in preadolescents with a physical disability: The mediational role of behavioral autonomy, Journal of Consulting & Clinical Psychology , 2002, vol. 70 (pg. 96-110)

35 Dellenmark-Blom M, et al. The esophageal-atresia-quality-of-life questionnaires: feasibility, validity and reliability in Sweden and Germany. J Pediatr Gastroenterol Nutr. 2018;67(4):469–77.



CHAPTER 7

Thoracoscopic traction technique in long-gap esophageal atresia: entering a new era

David C. van der Zee, Gabriele Gallo, Stefaan H. A. Tytgat

Surgical Endoscopy 2015 Nov;29(11):3324-30.

ABSTRACT

Objective
To describe the evolution from delayed management of long-gap esophageal atresia to thoracoscopic treatment directly after birth without the placement of a gastrostomy.

Background
Long-gap esophageal atresia remains a challenge for pediatric surgeons. Over the years, several techniques have been described to deal with the problem of the distance between the proximal and distal esophagus. More recently, a traction technique has been advocated. With the advent of minimal invasive surgery, the thoracoscopic elongation technique has been developed.

Methods
Retrospective description of a single-center experience with the thoracoscopic treatment of patients with long-gap esophageal atresia over a 7-year period.

Results
Between 2007 and May 2014, 10 children with long-gap esophageal atresia were treated by thoracoscopic elongation technique. In two children, the procedure failed. Eight children successfully underwent thoracoscopic traction with delayed primary anastomosis. Initially, all patients had a gastrostomy. During the course, the technique evolved into delayed primary anastomosis directly after birth without the use of a gastrostomy.

Conclusion
Thoracoscopic elongation technique in long-gap esophageal atresia not only is feasible, but can nowadays also be performed directly after birth without the use of a gastrostomy. With this development, we have entered a new era in the management of long-gap esophageal atresia.

INTRODUCTION

Long-gap esophageal atresia remains a challenge for pediatric surgeons. Over the years, several techniques have been described to tack the problem of the distance between the proximal and distal esophagus. The incidence of long-gap esophageal atresia is so low that it is difficult for individual centers to gain large experience and most series published have anecdotal data.

A more recent developed technique is the open traction technique, first described by Foker[1], in which the two ends of esophagus are pulled toward each other by external traction over time to ultimately be anastomosed. The outcome is variable, and achievement of feeding is not undivided favorable[2,3]. With the advent of minimal invasive surgery and the increasing experience in the treatment of type C esophageal atresia, the thoracoscopic elongation technique became feasible. After a first description of the technique[4], we now describe our 7-year experience with the thoracoscopic traction technique and the development toward a procedure almost similar to the standard type C esophageal atresia.

MATERIALS AND METHODS

Evolution of technique

Initially, we started with performing a (laparoscopic) gastrostomy upon the diagnosis of long-gap esophageal atresia together with a Replogle suction tube in the proximal esophagus. Along the course, as we started the traction directly after birth, we no longer performed the gastrostomy, but only did a laparoscopic gastropexy against the anterior abdominal wall to prevent the stomach from migrating up into the thorax. We principally try to avoid an esophagostomy in the neck, because it will be more difficult to bring the esophagus back down into the thorax at a later stage, reducing the available techniques usually to a gastric pull-up or colon interposition.

Each procedure is started with a rigid tracheobronchoscopy as almost half of our patients turned out to have a proximal fistula. Depending on the level of the proximal fistula, this is managed either thoracoscopically or through the neck.

For the traction technique, the patient is positioned in a 3⁄4 left lateral position at the left side of the table, as we would do for the routine thoracoscopic anastomosis in type C esophageal atresia. A first 5-mm trocar is placed 1 cm anterior and below the tip of the scapula by incision in the skin and blunt perforation of the muscularis and pleura, respectively. In smaller children under the weight of 2,000 g, we increasingly use a 3-mm trocar for the optic. Thereafter, two 3-mm trocars are placed under direct vision in a triangle around the endoscope. All patients nowadays are operated upon under the surveillance of near-infrared spectrometry (NIRS) and a-EEG to monitor the brain oxygenation and activity, respectively. After insufflation with CO_2, at 3–5 mm Hg and a flow of 1 l/min, and adjustment of the ventilation by the anesthesiologist, it is started with mobilization of the proximal esophagus to a maximal extent in the thoracic aperture (Figure 1). If a proximal fistula is present, this is closed at the same instance.Thereafter, the distal esophagus is determined (Figure 2) and mobilized out of the esophageal hiatus.

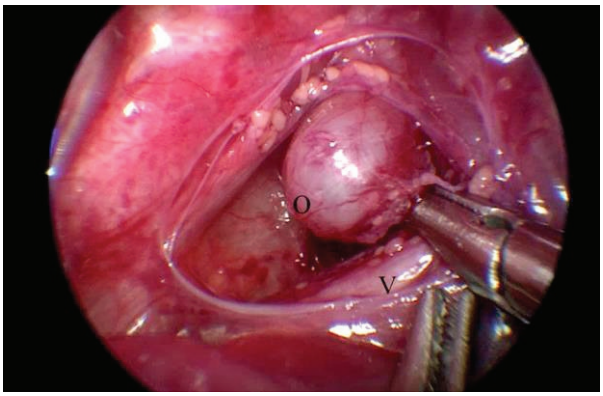


Figure 1 | Mobilization of proximal esophagus. *O = proximal esophagus, V = trachea with onlying vagal nerve*

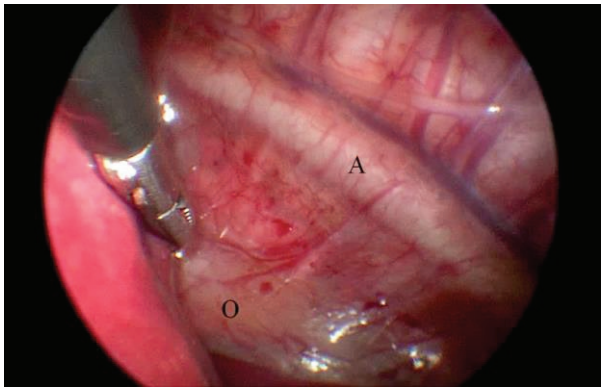


Figure 2 | Mobilization of distal esophagus out of hiatus. *O = distal esophagus coming through the esophageal hiatus, A = aorta*

Frequently, the hiatus has to be opened in order to retrieve the distal esophagus. The esophagus is mobilized as much as possible up to the fundus of the stomach. Principally, all patients will need an antireflux procedure at a later stage. Traction sutures Vicryl 4 9 0 (Ethicon, Johnson & Johnson, Amersfoort, NL) are introduced with the use of an Endo-close® (Covidien, Zaltbommel, NL), and bites of the esophagus are taken at four corners. Pledgets have not been used. Again with the Endoclose®, the sutures are crosswise withdrawn from the thorax and through a small piece of silicone tubing held with a mini-mosquito under traction. The same procedure is carried out on the other side. Close to both ends of the esophagus, a clip is applied to the sutures (Figure 3) to be able to determine the approximation over the coming days by thorax radiograms. Under direct vision, the traction is tested and the distance to be covered is determined.

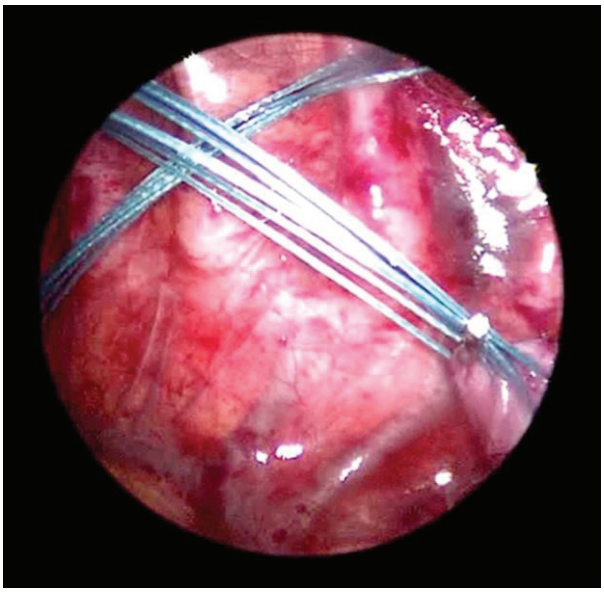


Figure 3 | Traction sutures with a clip close to the esophageal pouches

The procedure is then terminated. The 5-mm defect is closed with a Vicryl 5 9 0 muscular and subcutaneous suture, and all skin defects are approximated with Steristrips® (3 M, Zoeterwoude, NL). During the traction period, the patients remain intubated and sedated, but there is no need to be paralyzed. A diagram displays the principal of the procedure (Figure 4).

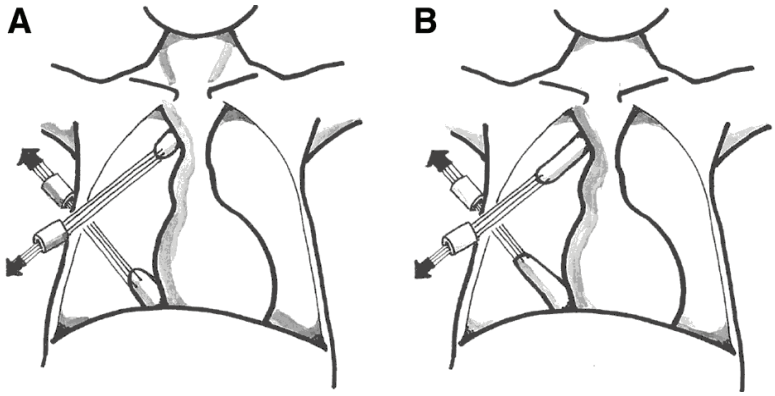


Figure 4 | Diagram of traction technique. *A Distance at start of traction. B Elongation of the two pouches over the days of traction*

Nowadays, the patient, that is referred without gastrostomy as well as the patient primarily born in our center, is then turned in a supine position, and a 5-mm trocar is introduced through the umbilicus by open technique. One or two additional 3-mm trocars are placed under direct vision. The (micro-)stomach is located, and the best spot is determined to perform a gastropexy against the ventral abdominal wall with two Ethibond 4 9 0 sutures (Ethicon, Johnson & Johnson, Amersfoort, NL) to prevent the stomach from migrating into the thorax.
A postoperative X-Thorax is made to determine the length of the defect (Figure 5), and the approximation is followed by daily radiograms.

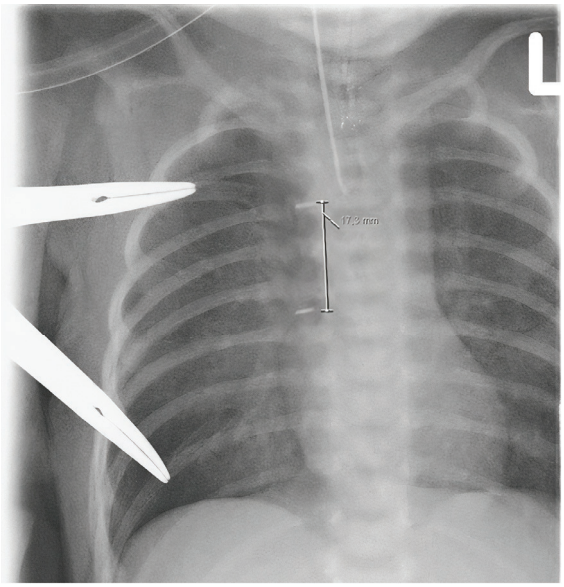


Figure 5 | X-thorax after application of traction sutures. *There is still a distance of 17.3 mm*

The traction sutures are checked twice daily, but unless there is a lot of mobility, the mosquitos are not adjusted and no additional traction is exerted, as too much traction will lead to disruption of the sutures. This detail is crucial in our opinion, because since having this restraining protocol, no more suture disruptions have occurred.
Usually, after 3–4 days, there is no more progression, due to adhesion formation between the esophagus and the adjacent lung. The child is then taken back into the operating theater, and thoracoscopic adhesiolysis is carried through by carefully sweeping loose the adhesions between esophagus and lung. Usually, there is still a too large gap between the two ends to safely perform a primary anastomosis. If necessary, the sutures can be led out at a higher level, and traction is installed again.
In general, after a total of 4–6 days, when the clips have approximated sufficiently (Figure 6), the patient can be taken back to theater for the delayed primary anastomosis.

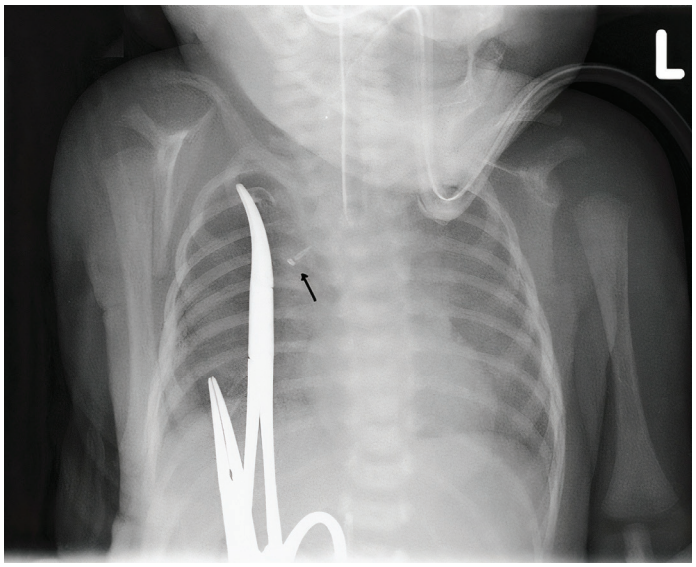


Figure 6 | X-thorax after 5 days. *The clips of the proximal and distal pouch have reached each other (arrow)*

After mobilization of the two ends, two or sometimes three traction sutures can be applied at the corners and posterior wall of the two pouches, before opening the proximal and distal esophagus, and the two ends can be advanced by the sliding technique. One or two additional sutures can be laid on the posterior wall before a 6– 8F gastric feeding tube is advanced into the distal esophagus and stomach (Figure 7).

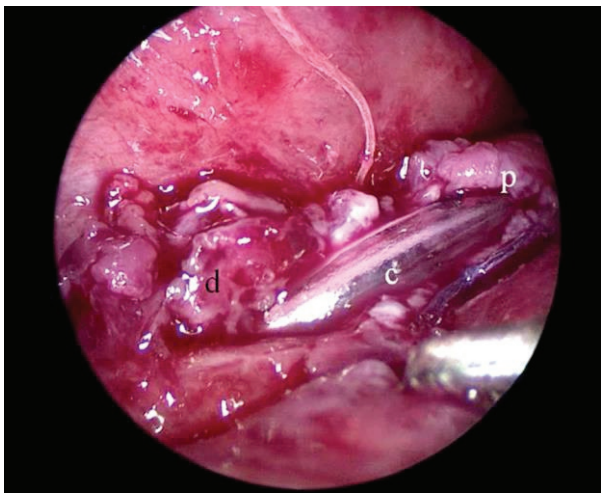


Figure 7 | Advancing nasogastric tube after anastomosis of posterior wall. *p = proximal esophagus, d = distal esophagus, c = feeding tube*

Sometimes the mucosa in the distal esophagus has not advanced as much as the muscularis, and the distal esophagus has to be incised further to identify and open themucosa. This can hamper making a solid anastomosis.
Principally, a drain is only left behind if there is doubt that the anastomosis is 100 % watertight.
A contrast swallow study is performed at day 5. When there is no leakage, oral feeds can be started. In patients that have a micro-stomach, this can be difficult, and in those cases, often it has to be started with continuous drip feeding giving the stomach time to adjust and grow.
In case there is no advancement or when complications occur, such as perforation, the technique is abandoned, and management is switched to alternative procedures like jejunal interposition or gastric pull-up, in case the proximal esophagus is too high up in the thorax or the neck.
Principally, all children will need a laparoscopic fundoplication after 4–6 weeks. The study was approved by the hospital medical ethical committee.

RESULTS

Between 2007 and May 2014, 10 children were either admitted or transferred to our department for treatment of their long-gap esophageal atresia. Gestational age varied from 30 4/7–40 1/7 weeks (*M* = 34 4/7). Weight at time of birth varied from 1,395 to 3,850 g (*M* = 2,330 g). Age at time of operation varied from 2 days to 6 months (Table 1). In four patients, a proximal fistula was detected during preoperative tracheoscopy. In two cases, the fistula could be closed thoracoscopically, the two others were too high and were dealt with through the neck. Initially, the patients either received a gastrostomy or were referred with a gastrostomy and a Replogle tube in the proximal esophagus. As of the fifth case, we no longer performed a gastrostomy, but kept the patient on parenteral nutrition during the elongation period. The first time we performed the procedure without gastrostomy, we encountered that after 2 days, the two pouches could be easily anastomosed, but that the stomach had migratedvpartially into the thorax. We thereafter prophylactically performed an anterior gastropexy against the anterior abdominal wall to prevent the stomach from going up into the thorax. The first time, however, we experienced that the Vicryl 5 9 0 suture we used had partially dissolved when performing the laparoscopic antireflux operation 6 weeks later. We since then use Ethibond 4 9 0 to fix the stomachagainst the anterior abdominal wall.

In two cases in the early experience, the traction sutures have torn out during the traction procedure and had to be replaced. It was therefore decided not to apply additional traction on the sutures during the elongation, unless there was evidently no tension on the sutures any longer, in order to prevent disruption by pulling too hard. Since restraining the protocol, no more suture ruptures have occurred. In one 1,710-g child, after 5 days, the end of the pouches seemed partially frayed by the past traction, still leaving approximately 1-cm bridge to gap during anastomosis. The child, however, recovered well with no leakage at the contrast study after 5 days. In four additional cases, there was no further advancement after 3 days, and we had to go back to perform adhesiolysis to facilitate further traction. In one of these children, the clip of the distal pouch had reached the thoracic wall and during this procedure was replaced two ribs higher (Table 2).

In one child, there was no more advancement after5 days, and we had to undo the anterior gastropexy in orderto gain more length and make the primary delayed anastomosis. At this time, this did not have any negative effecton the abdominal position of the stomach, as could bedetermined during the antireflux procedure 6 weeks later. In two patients, the elongation procedure failed. The first time was a patient, where we only minimally dissected thetwo pouches before applying the traction sutures, reasoningthat if induced growth, as was suggested by Foker, was thecrucial factor in elongation, then minimal dissection wouldsuffice and reduce the risk of compromised perfusion.However, no gain of length was achieved, and eventuallythe sutures were torn out of the distal esophagus, and therewas an open connection with the lumen. The procedure was the esophagus. It was then decided how to approach the defect. In some patients, a delayed primary anastomosis could be attempted, and in others, it was chosen for esophageal replacement by gastric pull-up, jejunal or coloninterposition[5–7].

There has been ongoing discussion if the native esophagus is not the best option for restoring the continuity. In 1997, Foker described his external traction technique. He hypothesized that the native esophagus would grow under stimulation of traction[8]. If that would be the case, this growth would be exceedingly fast. In our second patient, we only minimally dissected both ends of the esophagus, in order to let growth take place without compromising the circulation during extensive dissection. However, there wasonly minimal stretching without any progress as suggested by Foker. We therefore doubt that growth will be of any important influence in the advancement of both ends of therefore abandoned, and the patient underwent a jejunal interposition. In the second patient, there was an accidental perforation of the proximal pouch with the Replogle tube by the anesthesiologist during dissection. The perforation was closed, and traction sutures could be applied. In the days thereafter, the two pouches approached satisfactorily, until after 3 days during changing endotracheal tube plasters, the Replogle tube was accidentally advanced, and again caused a perforation of the proximal esophagus. On re-exploration, there was contamination of the mediastinum, and the distance was still too large to be bridged. As the upper pouch was high up in the thorax aperture, it was decided to perform a gastric pull-up.

Postoperatively, in two children, there was some minor leakage for which a drain was placed for 3 days. The others could start drinking 5 days postoperatively. The children could be discharged 14–20 days postoperatively, meaning that the last four patients that were treated without gastrostomy could be discharged at the age of 16–21 days.

In the follow-up, all but one children had gastroesophageal reflux requiring dilatation and underwent a laparoscopic antireflux procedure after 4–6 weeks. Three children additionally needed balloon dilatation thereafter, but are now free of symptoms. Two children suffered from life-threatening events due to severe tracheomalacia and underwent a thoracoscopic aortopexy. All children grow and eat according to their age.

Table 1 | Demographics of patients with long-gap esophageal atresia

Patients	2007–May 2014
No.	10
Boys	6
Girls	4
Gestational age	30 4/7–40 1/7 weeks (mean 34 4/7)
Birth weight	1,395–3,800 g (mean 2,330 g)
Associated congenital anomalies	AVSD 1, ARM 2

AVSD atrium-ventricular septum defect, ARM anorectal malformation

Table 2 | Distance between proximal and distal esophagus after maximal traction

Patient	Distance in no. vertebrae after maximal traction	Distance in mm between clips after maximal traction
1	3	21.6
2	5	35.8
3	4	29.8
4	3	23.9
5	2	11.9
6	3.5	21.5
7	3	19.1
8	3	19.6
9	3	17.0
10	3.5	24.5

DISCUSSION

Long-gap esophageal atresia has always been a challenge for the pediatric surgeon. In the past, initially all patients were given a gastrostomy for feeding. During the follow-up after 2–6 months, a contrast study could be performed to determine the distance between proximal and distal end of esophagus. Length will primarily be gained by traction and distraction. In all the other patients that underwent the thoracoscopic elongation technique, sufficient length was achieved within 4–6 days of traction. In our ninth patient, elongation did not extend further than 5 days. Prolonged traction did not lead to further gain of length, and during the procedure for restoring continuity, the anterior gastropexy was released in order to gain more length. Although our experience is still limited, we do not believe that traction longer than approximately 10 days will be adding anything in the gaining of length. What is important is the fact that the tissues of esophagus and lungs will adhere in due time.

In open surgery, all kinds of silicone sheeting are used to avoid adhesion formation. In the thoracoscopic approach, this is not feasible, and keeping the procedure as simple as possible, after 3–4 days when no more progression is seen, renewed thoracoscopy is performed to carefully release the adhesions and ascertain that the traction sutures are still effectively in place, as was the case in threepatients. Another issue is what kind of sutures should be used and how deep the bites should be taken. Surely one can take superficial 6 9 0 sutures, using pledgets to protect the tissue from tearing, but this will carry the risk that the underlying mucosa will not advance likewise. Even when using Vicryl 4 9 0 sutures, taking good bites, in two cases we encountered retraction of the mucosa in the distal esophagus. In one case, we could introduce a dilator through the gastrostomy and advance the mucosa for suturing, and in the other, we had to incise the distal esophagus over 1 cm to retrieve the mucosa.

In our experience, it has particularly been the distal esophagus that could be elongated. The proximal end extended either only slightly or none at all. Taking into account the fact that the fetus has been trying to swallow its amniotic fluid throughout pregnancy, it seems logical that the proximal esophagus has already been stretched maximally and that not much gain is to be expected, apart from releasing a proximal fistula. We therefore have some reservation as to the Kimura technique[9]. Mobilizing the proximal esophagus into the neck and trying to elongate it is an extensive procedure, not only in time, but also bringing it back into the thorax, not to speak of the discomfort for the patient. Externalizing the esophagus into the neck will make a secondary intrathoracic anastomosis, with either the distal esophagus or an interpositioned jejunum, more difficult. Nowadays, continuous suction with a Replogle tube is a well-accepted method[10].

As the long-gap esophageal atresia repair is complicated, usually time is bought by creating a gastrostomy for enteral feeding and letting the child grow, before an attempt is made to perform a delayed primary repair or the interposition of either stomach, jejunum or colon. Before starting on the thoracoscopic elongation technique, extensive experience was achieved with the thoracoscopic correction of type C esophageal atresia[11]. Dealing with these cases, we also encountered patients where the distance between the proximal and distal pouch extended over

several centimeters. With the use of sliding knot suture technique, we managed to approximate these esophageal ends to make a sufficient anastomosis. All these procedures were carried out in neonates, the smallest weighing only 1,000 g. We therefore saw no restrictions to start the thoracoscopic elongation in neonates as well. This series has demonstrated that neonates tolerate the procedure well. The smallest child weighed 1,600 g at the time of thoracoscopic elongation. Initially, we also started with giving the patients a gastrostomy. However, in many instances, the gastrostomy had to be taken down in order to facilitate a laparoscopic antireflux procedure 4–6 weeks later. As we started to perform the procedure in the first week of life, we decided to not place a gastrostomy any longer. In our first case, this ended with the stomach being pulled up into the thorax. In the past, it had always been the gastrostomy that had kept the stomach in place. In the following patient, an anterior gastropexy was performed laparoscopically with Vicryl 4 9 0 sutures. This efficiently kept the stomach down. However, on carrying out the laparoscopic antireflux

procedure, we saw that the resorbable sutures in time had more or less been dissolved, leaving only fibrous bands between stomach and anterior abdominal wall. We thereafter changed to using Ethibond 4 9 0 non-resorbable sutures. So far this has efficiently kept the stomach down, even to such an extent that we had to release the gastropexy in our last patient in order to gain some more length to be able to make the anastomosis. Although this may seem contradictory, the benefits from making a watertight esophageal anastomosis outweigh the risk for a hiatal hernia that has to be corrected during the antireflux procedure.

The next issue to deal with after fulfilling the anastomosis is gastroesophageal reflux. Due to the traction, the gastroesophageal transition is stretched and pulled up into the thorax, undoing all antireflux properties. In spite of antireflux medication, and probably also due to marginal circulation, stenosis occurs, requiring dilation. Usually, the first dilation is planned for two weeks after the anastomosis, using a 8-mm dilation balloon, the second after 4 weeks using a 10 mm balloon, followed by an antireflux procedure. This may be challenging, because most of these patients have a micro-stomach, leaving little room for making a proper wrap. Important first step is to bring back the distal esophagus into the abdomen and narrowing the hiatal hernia. A one-step "mini" anterior wrap is created by approximating the anterior stomach wall against the esophagus at the level of the diaphragm and the diaphragm itself, instead of the usual two-step layer to create a sufficient length of intra-abdominal esophagus. Delaying the antireflux procedure for 4–6 weeks has two reasons: first, when the child is somewhat older, the tissues are less friable, and second, it will reduce the duration of the initial operation considerably.

Feeding in children with long-gap esophageal atresia may be an issue. From one part, the small stomach only has a limited capacity which is not enough for adequate growth. Some of these children need to be on tube feeding for a prolonged period until the stomach has grown sufficiently and/or when solid feeds become possible. The children operated in the neonatal period could start drinking within 1–2 weeks after correction, although in some, the frequency remained on eight feeds for a longer time due to the small stomach. This early start reduces many

of the feeding problems described after delayed start of feeding[3]. As soon as more solid food can be introduced, reflux, due to the limited capacity of the stomach, will be less obvious and sufficient energy intake becomes easier. Close collaboration with the dietician is important, and intake should be tailored to the individual patient.

More recently, there have been publications pointing out the negative side effects of anesthesia and surgery on neonates[12,13]. This is also one of the reasons why antireflux surgery is delayed for 4–6 weeks. Currently, all patients are operated on under surveillance of NIRS and a-EEG to monitor cerebral oxygenation and brain activity. The outcomes look promising, but will be published in the near future.

In conclusion, management of long-gap esophageal atresia seems to have taken a substantial step forward. Thoracoscopic treatment of long-gap esophageal atresia not only is feasible, but also facilitates treatment in the neonatal period without the need for a gastrostomy and a hospitalization time approaching that of standard esophageal atresia and that seems more determined by prematurity and weight, than the surgical management itself.

ACKNOWLEDGMENTS
We would like to thank Pieter Dik for the diagram on esophageal elongation.

REFERENCES

1 Foker JE, Linden BC, Boyle EM Jr, Marquardt C (1997) Development of a true primary repair for the full spectrum of esophageal atresia. Ann Surg 226:533–541; discussion 541–54

2 Sroka M, Wachowiak R, Losin M, Szlagatys-Sidorkiewicz A, Landowski P, Czauderna P, Foker J, Till H (2013) The Foker technique (FT) and Kimura advancement (KA) for the treatment of children with long-gap esophageal atresia (LGEA): lessons learned at two European centers. Eur J Pediatr Surg 23:3–7

3 Khan KM, Krosch TC, Eickhoff JC, Sabati AA, Brudney J, Rivard AL, Foker JE (2009) Achievement of feeding milestones after primary repair of long-gap esophageal atresia. Early Hum Dev 85:387–392

4 van der Zee DC, Vieirra-Travassos D, Kramer WL, Tytgat S (2007) Thoracoscopic elongation of the esophagus in long-gap esophageal atresia. J Pediatr Surg 42:1785–1788

5 Stone MM, Fonkalsrud EW, Mahour GH, Weitzman JJ, Takiff H (1986) Esophageal replacement with colon interposition in children. Ann Surg 203:346–351

6 Spitz L (1992) Gastric transposition for esophageal substitution in children. J Pediatr Surg 27:252– 257; discussion 257–259. Review

7 Bax KM (2009) Jejunum for bridging long-gap esophageal atresia. Semin Pediatr Surg 18:34– 39

8 Foker JE, Kendall Krosch TC, Catton K, Munro F, Khan KM (2009) Long-gap esophageal atresia treated by growth induction: the biological potential and early follow-up results. Semin Pediatr Surg 18:23–29

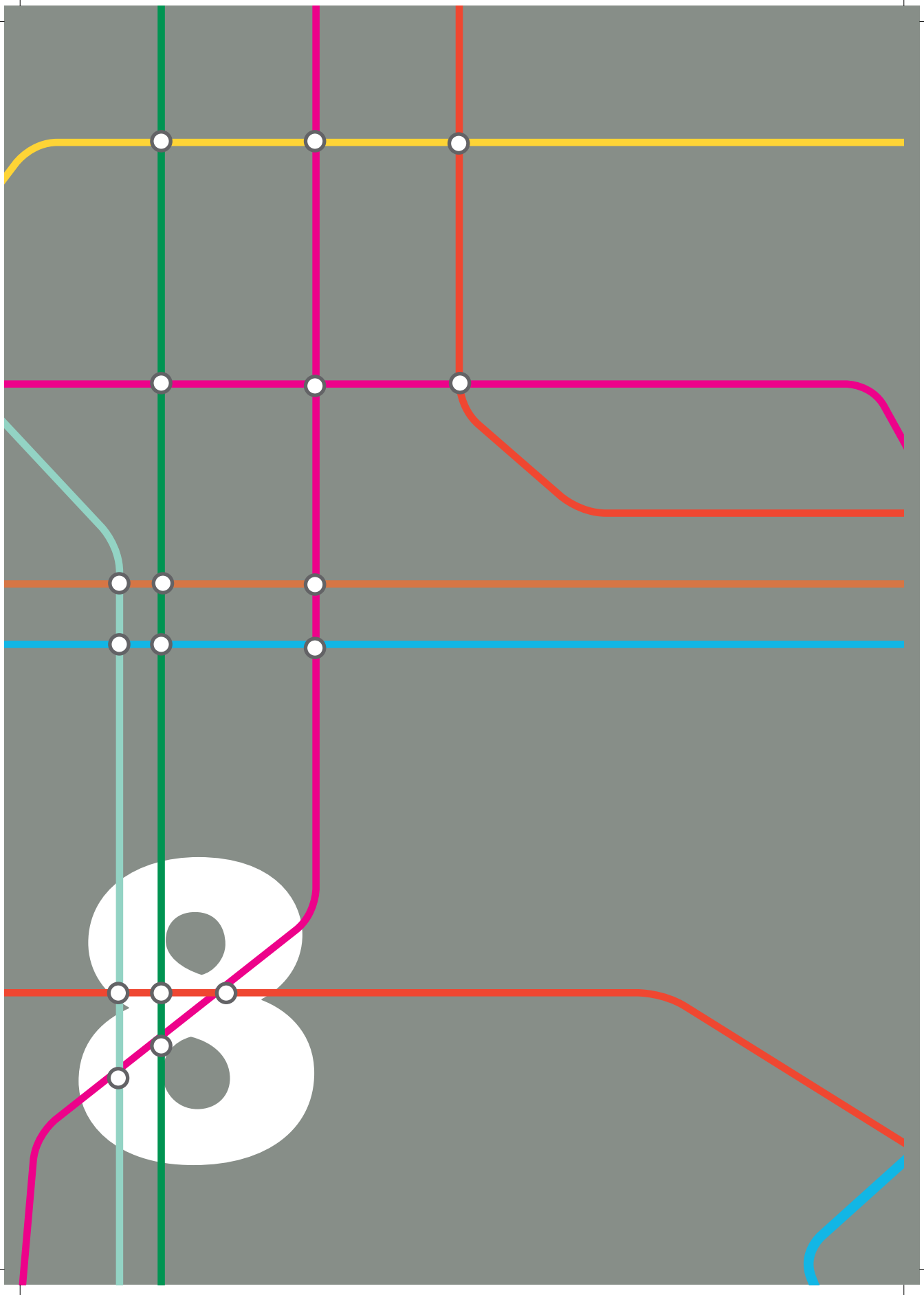
9 Kimura K, Soper RT (1994) Multistaged extrathoracic esophageal elongation for long-gap esophageal atresia. J Pediatr Surg 29:566–568

10 Aziz D, Schiller D, Gerstle JT, Ein SH, Langer JC (2003) Can 'long-gap' esophageal atresia be safely managed at home while awaiting anastomosis? J Pediatr Surg 38:705–708

11 van der Zee DC, Tytgat SH, Zwaveling S, van Herwaarden MY, Vieira-Travassos D (2012) Learning curve of thoracoscopic repair of esophageal atresia. World J Surg 36:2093–2097

12 Sanders RD, Hassell J, Davidson AJ, Robertson NJ, Ma D (2013) Impact of anaesthetics and surgery on neurodevelopment: an update. Br J Anaesth 110(Suppl 1):i53–i72

13 Lemmers PM, Molenschot MC, Evens J, Toet MC, van Bel F (2010) Is cerebral oxygen supply compromised in preterm infants undergoing surgical closure for patent ductus arteriosus? Arch Dis Child Fetal Neonatal Ed 95:F429–F434



CHAPTER 8

Summary and general discussion

Long-gap esophageal atresia (LGEA) is a rare congenital malformation of the esophagus that requires surgical correction. LGEA repair is technically very challenging and frequently accompanied by complications such as leakage or stenosis. These complications can be very cumbersome. The search for the best possible surgical treatment is, therefore, a challenging, but necessary task.

This thesis aims to describe the surgical treatment and the (postoperative) sequelae of patients with long-gap esophageal atresia (LGEA) in the Netherlands. Until recently, surgical correction for LGEA in the Netherlands was performed with a Gastric Pull-Up (GPU) or a Jejunal Interposition (JI). Both techniques have their advantages and disadvantages. To answer the question which technique offers the best results, we performed a meta-analysis of the available literature and several comparative studies.

Chapter 1 offers a general introduction of esophageal atresia, LGEA, the different techniques to bridge the long-gap and an overview of the different studies in this thesis.

Outcome of esophageal replacement (ER) for LGEA

Esophageal replacement (ER) in childhood is a major challenge. Several techniques of ER have been developed, such as GPU, JI and colon interposition (CI). Attempts to use synthetic grafts have failed[16]. Stomach, small bowel and colon replacement have been successfully performed in children[8]. There is still no consensus regarding the optimal surgical approach for LGEA.

Chapter 2 describes the results of a meta-analysis in order to find this optimal surgical LGEA correction. Of the 470 patients that were included by analyzing 15 studies on ER, there was no surgical approach that emerged as the most optimal technique. GPU and CI seemed comparable regarding anastomotic complications and graft loss. Only Tannuri et al showed lower numbers of necrosis of their colon conduit. This could possibly be explained by the fact that they have a vast experience in this type of ER and that they perform the colon conduit with a double blood supply[17]. Our meta-analysis showed that during longterm follow GPU seemed to be associated with a higher respiratory morbidity rate, whereas CI showed more longterm gastrointestinal complaints. Only two series provided data about JI and they showed opposing results. Bax et al9 showed less leakage and graft necrosis after JI compared to previous publications[18].

GPU versus JI follow up

In order to determine which type of ER is the better technique for the correction of LGEA, we compared the shortterm and midterm outcome of GPU versus JI in Chapter three. Our data demonstrated no mortality, but significant morbidity after both procedures. In one-third of the patients a re-intervention was required after both GPU and JI9,[18,19,20]. Anastomotic complications including leakage, stenosis and functional obstruction were significantly more reported after JI. This is in line with results of previous studies on GPU and JI. During follow up (median age 14 years) gastrointestinal complaints were reported by a vast number of patients after both procedures. There seemed to be a tendency toward more reflux complaints after GPU. This is comparable to other follow up studies evaluating reflux symptoms in adolescents and adults12. In our study we

found that patients after JI seemed to tolerate oral feeding better than GPU patients. In 44% of the GPU patients the weight for age was below -2SD compared to 26% of the JI patients.
We therefore conclude that GPU and JI are both ER techniques with significant morbidity. JI seems to have more complications shortly after surgery, whereas GPU shows more concerns during follow up.

Respiratory morbidity
Several studies have shown that respiratory-related quality of life is lower and daily respiratory problems occur more frequently after primary repair of EA with a distal TEF compared to healthy controls[21-22].
However, little is known about pulmonary function after ER.
Chapter four showed that respiratory complaints occurred in the majority of all LGEA patients after both procedures. However, asthma-like symptoms, dyspnea on exertion seemed to occur more frequently after GPU. There are no studies available comparing GPU versus JI. However, when solely comparing the results of our GPU cohort to other studies, we found that the prevalence of respiratory problems after GPU was higher than of healthy controls and primary EA repair patients[23]. Lung function tests in our study showed impairment both after GPU and JI when compared to healthy controls. However, lung function parameters in JI-patients were closer to controls than those of GPU-patients. Patients after GPU demonstrated a decrease in total lung capacity (TLC) compared to JI-patients, showing mainly a restrictive ventilatory disorder. This could be related to the space-occupying organ in the chest which may have limited normal lung development. It may also have been caused by damage to the lungs due to prolonged exposure of gastric reflux[24], since reflux symptoms were present in the majority of GPU patients (Chapter 5).
We conclude that respiratory problems and impaired lung function are worse after GPU than JI. Respiratory follow in adult life is important, especially in GPU patients.

Graft changes
After performing a GPU or JI, anatomical and mucosal changes of the grafts can be expected in time. In Chapter 5 we investigated these changes on a macro-and microscopic level in adolescent and young adults. Also, long term gastrointestinal symptoms were evaluated, showing that the majority of GPU patients had reflux complaints. This is in line with previous studies on GPU[25]. The JI patients had less reflux symptoms than the GPU patients, however postoperative dysphagia was present in the majority of JI patients. Also, the majority of JI patients had a dilated JI graft. Despite the dysphagia and dilated JI graft, all JI patients had full oral intake. This is in contrast to previous studies[18].
In 22% of GPU patients intestinal metaplasia was found. The importance of this finding is unclear, but concern may arise regarding the potential development of Barrett's esophagus in these patients. These histological changes were not associated with reflux symptoms. Therefore, reflux symptoms cannot be used as a reliable detector of mucosal changes. This is in line with previous studies[16]. Increased awareness with clinical and endoscopic surveillance for LGEA patients with ER is recommended, especially after GPU.

In **Chapter 5** we further showed that one third of the GPU patients was still underweight, as was also described in **Chapter 2**. Contrary, JI patients showed an increase in their weight over time.

Quality of Life (QOL)

Long term morbidity for LGEA appears to be significant[8]. Consequently, this morbidity may lead to a decrease in QoL. Only a few studies have investigated QoL after GPU and mostly without using validated tools[14,15]. QoL after JI has never been analyzed before.

In **Chapter 6** we focused on HRQoL using validated questionnaires. We found that generic and disease specific QoL in the majority of patients after ER was comparable to healthy controls. This finding is supported by several other publications[25]. There are two studies stating that QOL is diminished after ER[26,27]. However, these comprise complicated EA repairs and/or CI grafts.

When comparing GPU to JI patients, we found no differences in (HR)QoL. In both groups postoperative morbidity and re-intervention were not associated with changes in (HR)QoL.

These findings suggest that physical complaints after ER have no effect on the perception of the well-being of these patients. Also, patients and their families may have developed efficient coping strategies in order to face the challenges of life after ER.

A disease-specific QOL tool has been developed recently by Dellenmarck et al[28]. Currently, a translation of this questionnaire is being validated in the Netherlands. Hopefully, this may provide more detailed information on well-being of EA patients in the near future.

Novel native esophagus-preserving techniques

Recently the INoEA has published that the native esophagus should be preserved when correcting LGEA[6]. Esophageal continuity via delayed primary anastomosis can cause swallowing difficulties due to postponed oral feeding and prolonged hospital stay[29].

Esophageal continuity with thoracoscopic traction technique (TTT) offers the opportunity to perform a primary anastomosis within days after birth. In **chapter 7** we introduced the TTT as a novel strategy for LGEA. Eight out of ten children successfully underwent TTT and after four to six days of elongation a thoracoscopic delayed primary anastomosis could be performed.

In two children the procedure failed and ER with GPU and JI was performed.

Due to the traction, the gastroesophageal junction is stretched and pulled up into the thorax, undoing all antireflux mechanisms. Therefore, four to six weeks after performing the primary anastomosis antireflux surgery is fashioned by laparoscopic fundoplication.

We conclude that thoracoscopic elongation technique is a feasible native esophagus-preserving procedure for the treatment of LGEA. Traction can be performed directly after birth, without need of gastrostomy and has a limited hospitalization time.

DISCUSSION

Esophageal Replacement (ER) in long-gap esophageal atresia (LGEA) is a feasible bridging technique. Taking in account the advantages and disadvantages of the different types of ER, we conclude that not one single type can be pointed out as the best technique. However, we were able to identify several aspects of ER that stood out in the different chapters in this thesis.

First, Jejunal interposition (JI) seemed to be associated with more short-term postoperative morbidity, such as e.g. anastomotic leakage, stenosis and functional obstruction. This may be caused the fact that JI is a technically complicated procedure and has a very precarious blood supply. This can result in ischemia of the anastomosis. Not many surgeons are skilled enough to perform this procedure. That is why there is a lack of studies on this technique and existing outcome varies between centers.

Despite the early morbidity of JI, the long-term outcome of JI regarding feeding, growth, gastrointestinal and respiratory complaints is more favorable compared to the Gastric pull-up (GPU) technique. Although the GPU seems to have less short-term postoperative complications, persisting of gastroesophageal reflux causes long term morbidity of the respiratory tract and gastro-intestinal. Gastrointestinal morbidity is manifested in different aspects. One of these aspects is a decrease in growth of LGEA patients after GPU compared to JI patients. This may be due to the anatomical and functional changes of the stomach transposed into the mediastinum. The stomach plays a crucial role in the mechanism of food digestion. Stretching and transposing an organ with such a complex function into the mediastinum may negatively affect this process of food digestion. Food intake and growth, therefore, deserve attention during follow up. The role of dieticians appears crucial in the multidisciplinary outpatient care of LGEA.

Another aspect of gastrointestinal morbidity is formed by changes to the mucosa of the esophagus. Intestinal metaplasia is found in 22% of GPU. It is not clear if this finding will lead to actual Barrett's esophagus or ultimately even carcinoma. Multiple cases of esophageal carcinoma have been described in EA patients[12,13]. Endoscopic surveillance has been recommended by the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPHGAN)-North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPHGAN) guidelines. A recent study by ten Kate et al30, showed that endoscopic surveillance of EA patients, including those with a colon interposition, can be started at 20 years of age. These recommendations concern mostly patients after primary repair of EA. We believe that a more intensive surveillance programme may be required for patients after GPU considering the high prevalence of gastroesophageal reflux.

Regarding respiratory morbidity, GPU patients develop more symptoms during follow up. This is partially due to persisting reflux. Ofcourse tracheomalacia may also play an important role, as in all EA patients[5]

Despite the respiratory and gastrointestinal morbidity after ER, Quality of life is not compromised in these patients. Patients seem to have developed efficient coping strategies or may have gotten used to respiratory and/or gastrointestinal symptoms. This is also found in children with a chronic illness, such as cystic fibrosis, diabetes mellitus and asthma in a previous study by Meijer et al[31].

Although ER for LGEA is a feasible technique, esophagus-preserving techniques are on the rise. According to a recent study by INoEA, preserving the native esophagus should be considered the first step in approaching LGEA in the future. The thoracoscopic elongation technique entails correcting LGEA by performing traction on the native esophagus directly after birth. With this TTT, there is no need for a gastrostomy and hospital stay is reduced. Although the TTT emerges as a promising novel technique, it is exclusively performed in selected highly-expertise centers, whereas ER is performed in different Center of Expertise (CoE) worldwide. Consequently, limited data are available, rendering comparison difficult. Pilot data however, show that anastomotic leakage, stenosis and reflux occur after TTT, as is described in ER. As TTT is increasingly being performed, more data and long term follow up will become available. Then, future well-designed studies will hopefully provide evidence on the best surgical approach for LGEA correction.

The main limitations of this thesis are the retrospective nature of the studies and the small sample sizes. Because of the small numbers, comparison is difficult and statistical analysis may result in outcomes that are over- or underestimated.
This small size in patient numbers is difficult to tackle. A strategy to handle this problem, could be to centralize all LGEA patients to a limited number of CoE's and to stimulate cooperation between these CoE's. Then, all available ER and esophagus-preserving techniques would be mastered between these CoE's. We expect that after collecting the data of this conglomerate of CoE's, well-designed randomized trials can be set up and executed. Consequently, the best surgical approach to treat LGEA can then be identified.

REFERENCES

1 Sfeir R, Michaud L, Sharma D, Richard F, Gottrand F. National esophageal atresia register. Eur J Pediatr Surg 2015;25:497–9. doi: 10.1055/s-0035-1569466 .

2 Pedersen RN, Calzolari E, Husby S, Garne E; EUROCAT Working 2012;97(03):227–232

3 Epidemiology of esophageal atresia. Sfeir R, Michaud L, Salleron J, Gottrand F. Dis Esophagus. 2013 May-Jun;26(4):354-5. doi: 10.1111/dote.12051. PMID: 23679022

4 IJsselstijnH, GischlerSJ, ToussaintL, et al.Growth and development after oesophageal atresia surgery:need forlong-term multidisciplinary follow-up.PaediatrRespirRev. 2016;19:34–38

5 van der Zee DC, van Herwaarden M, Hulsker C, et al. Esophageal Atresia and Upper Airway Pathology. Clin Perinatol 44 (2017) 753–762

6 van der Zee DC, Bagolan P, Faure C, Gottrand F, Jennings R, Laberge JM, et al. Position paper of INoEA working group on long-gap esophageal atresia: for better care. Front Pediatr 2017;5:2–4. doi: 10.3389/fped.2017.0 0 063 .

7 Spitz L. Gastric transposition in children. Semin Pediatr Surg 2009;18(1):30–33

8 P. Loukogeorgakis , A. Pierro. Replacement Surgery for Esophageal Atresia. Eur J Pediatr Surg 2013; 23(03): 182-190 DOI: 10.1055/s-0033-1347915

9 Bax KM. Jejunum for bridging long-gap esophageal atresia. Semin Pediatr Surg 2009;18(1):34–39

10 Hamza AF. Colonic replacement in cases of esophageal atresia. Semin Pediatr Surg 2009;18(1):40–43

11 van der Zee DC, Gallo G, Tytgat SHA. Thoracoscopic traction technique in long-gap esophageal atresia: entering a new era. Surg Endosc 2015;29:3324–30. doi: 10.10 07/s0 0464-015-4091-3 .

12 Vergouwe FWT, IJsselstijn H, Biermann K, Erler NS, Wijnen RMH, Bruno MJ, Spaander MCW. High Prevalence of Barrett's Esophagus and Esophageal Squamous Cell Carcinoma After Repair of Esophageal Atresia. Clin Gastroenterol Hepatol 2018; 16: 513-521.e6. [DOI: 10.1016/J.CGH.2017.11.008]

13 Pultrum BB, Bijleveld CM, De Langen ZJ, Plukker JTM. Development of an adenocarcinoma of the esophagus 22 years after primary repair of a congenital atresia. J Pediatr Surg (e-pub ahead of print 2005; doi:10.1016/j.jpedsurg.2005.08.042).

14 Deurloo JA, Ekkelkamp S, Hartman EE, et al. Quality of life in adult survivors of correction of esophageal atresia. Arch Surg 2005;140:976–80.

15 S.P. Tan Tanny, et al., Quality of life assessment in esophageal atresia patients: a systematic review focusing on long-gap esophageal. J Pediatr Surgery, Available online 5 October 2019, https://doi.org/10.1016/j.jpedsurg.2019.08.040

16 Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP, Johnson F, Hongo M, Richter JE, Spechler SJ, J Tytgat GN, Wallin L. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification

17 Tannuri U, Maksoud-Filho JG, Tannuri AC, Andrade W, Maksoud JG.Which is better for esophageal substitution in children, esophagocoloplasty or gastric transposition? A 27-year experience of a single center. J Pediatr Surg 2007;42(3):500–504

18 Cauchi JA, Buick RG, Gornall P, SimmsMH, Parikh DH. Oesophageal substitutionwith free and pedicled jejunum: short- and long-term outcomes. Pediatr Surg Int 2007;23(1):11–19

19 Spitz L, Kiely E, Pierro A. Gastric transposition in children–a 21-year experience. J Pediatr Surg 2004;39(3):276–81 [discussion 276–81].

20 Hunter CJ, Petrosyan M, ConnellyME, Ford HR, Nguyen NX. Repair of long-gap esophageal atresia: gastric conduits may improve outcome-a 20-year single center experience

21 Sistonen S, Malmberg P, Malmström K, et al. Repaired oesophageal atresia: respiratorymorbidity and pulmonary function in adults. Eur Respir J 2010;36(5):1106–12.[11] Spitz L. Gastric transposition via the mediastinal route for infants with long-gap esophageal atresia. J Pediatr Surg 1984;19(2):149–54

22 Olbers J, Gatzinsky V, Jönsson L, et al. Physiological studies at 7 years of age in children born with esophageal atresia. Eur J Pediatr Surg 2014 [in press]. 10.1055/s-0034-1390017.

23 Jönsson L, Friberg LG, Gatzinsky V, et al. Treatment and follow-up of patients with long-gap esophageal atresia: 15 years' of experience from the western region ofSweden. Eur J Pediatr Surg 2015;5 [in press]. 10.1055/s-0034-1396415

24 Malmström K, Lohi J, Lindahl H, et al. Longitudinal follow-up of bronchial inflammation, respiratory symptoms, and pulmonary function in adolescents after repair of esophageal atresia with tracheoesophageal fistula. J Pediatr 2008;153:396–401.

25 Hannon E, Eaton S, Curry JI, Kiely EM, Spitz L, De Coppi P. Outcomes in adulthood of gastric transposition for complex and long-gap esophageal atresia. J Pediatr Surg 2020; 55: 639–645. [PMID: 31519362 DOI: 10.1016/j.jpedsurg.2019.08.012]

26 Dingemann C. Long-term health-related quality of life after complex and/or complicatedesophageal atresia in adults and children registered in a German patient supportgroup. J Pediatr Surg. 2014;49(4):631–8.

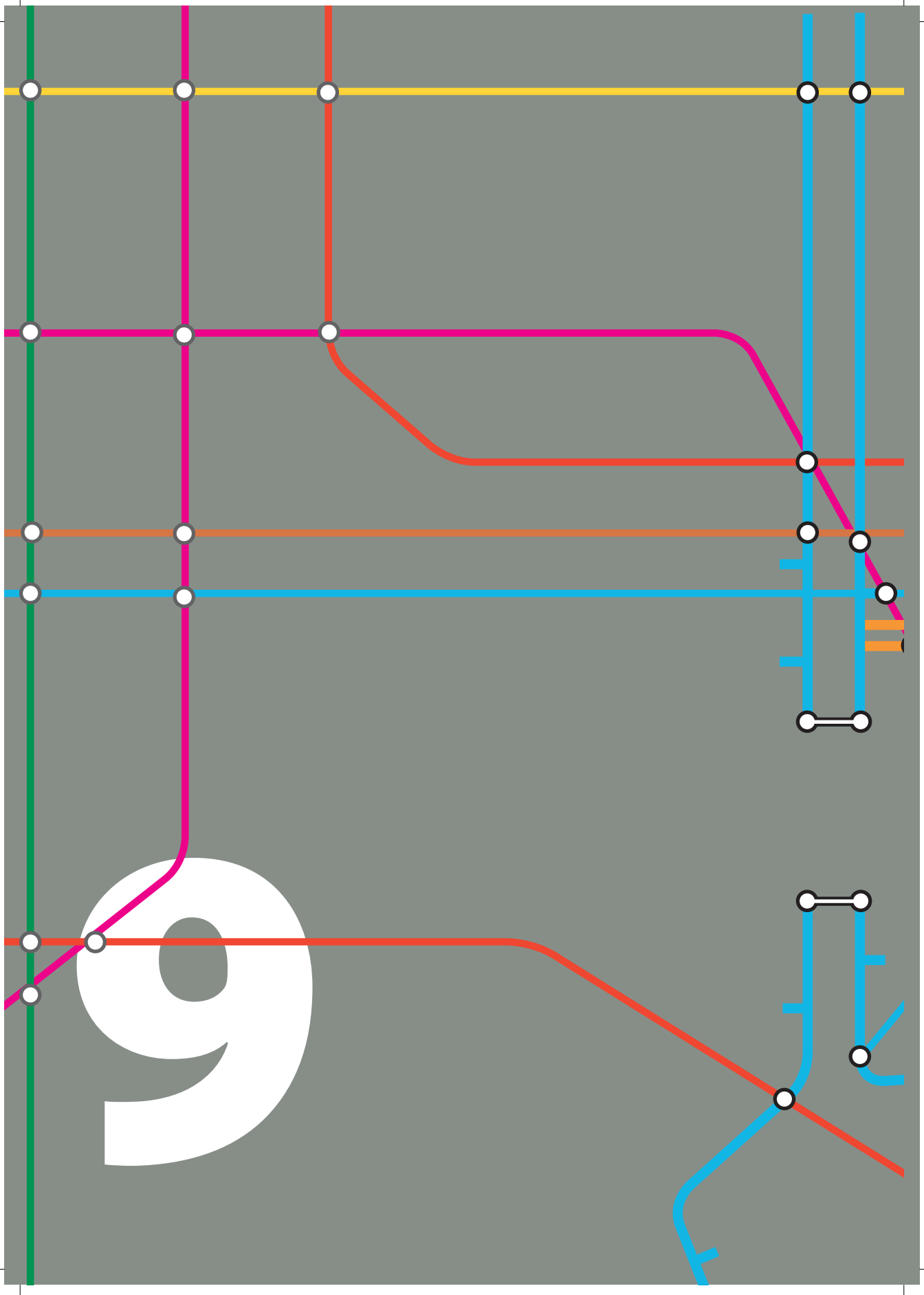
27 Tan Tanny SP, et al. Quality of life assessment in esophageal atresia patients: a systematic review focusing on long-gap esophageal. J Pediatr Surg. 2019. https://doi.org/10.1016/j.jpedsurg.2019.08.040.

28 Dellenmark-Blom M, et al. The esophageal-atresia-quality-of-life questionnaires:feasibility, validity and reliability in Sweden and Germany. J Pediatr GastroenterolNutr. 2018;67(4):469–77.

29 van Tuyll van Serooskerken ES, Lindeboom MYA, Verweij JW Childhood outcome after correction of long-gap esophageal atresia by thoracoscopic external traction technique. J Pediatr Surg 2021 Oct;56(10):1745-1751. doi: 10.1016/j.jpedsurg.2021.05.001

30 Ten Kate CA, van Hal ARL, Erler NS et al.Recommendations for endoscopic surveillance after esophageal atresia repair in adults. Dis Esophagus . 2022 Jul 12;35(7):doab095. doi: 10.1093/dote/doab095.

31 Meijer, et al. Social functioning in children with a chronic illness. J Child Psychol Psychiatry. 2000;41(3):309–17.


9

CHAPTER 9

Dutch summary
Nederlandse samenvatting

De artikelen in dit proefschrift tonen de klinische resultaten van de twee oesophagus vervangende (OV) procedures voor long-gap oesophagus atresie (LGOA), aanbevolen door de INoEA (International Network of Oesophageal Atresia)[1]: maag transpositie (MT) en jejunum interpositie (JI). De gepresenteerde studies richten zich op vroege postoperatieve morbiditeit met de nadruk op anastomotische complicaties, langdurige gastro-intestinale functie en reflux, respiratoire morbiditeit, micro- en macroscopische veranderingen van de interponaten op lange termijn en kwaliteit van leven. Ook worden de eerste resultaten beschreven van de thoracoscopische tractie techniek (TTT), een natieve oesophagus-sparende procedure ontwikkelde in de laatste jaren.

Hoofdstuk 1 bevat een algemene introductie van oesophagusatresie (OA): klinische presentatie, (prenatale) diagnostiek en chirurgische behandeling. Specifieke aandacht wordt besteed aan LGOA met beschrijving van de operatie technieken van de OV procedures en TTT.

In **hoofdstuk 2** beschrijven we de resultaten van een meta-analyse van studies gepubliceerd tussen 2006 en 2011 betreffende de uitkomsten van OV procedures voor LGOA en refractaire oesophagus stricturen, met als doel de optimale OV procedure te identificeren. In deze studie werden de resultaten geanalyseerd van MT, JI en colon interponaat (CI). Geen van de chirurgische technieken kwam naar voren als de meest optimale procedure. MT en CI leken vergelijkbaar wat betreft anastomotische complicaties en necrose van het interponaat. Verder was MT geassocieerd was met een hogere respiratoire morbiditeit gedurende follow up, terwijl CI een hogeren gastro-intestinale morbiditeit toonde. Slechts twee series leverden data over JI en ze lieten tegengestelde resultaten zien. Bax et al.[2] toonden minder lekkage en graft necrose aan na JI in vergelijking met eerdere publicaties[3].

In **hoofdstukken 3** tot en met **6** presenteren we verschillende cohortstudies waarin LGEA-patiënten werden vergeleken na GPU of JI. We hebben er bewust voor gekozen om CI niet te includeren in dit proefschrift, omdat CI door de INoEA beschouwd wordt als een reddingsprocedure wanneer andere strategieën niet succesvol zijn gebleken[1]. Bovendien wordt CI in Nederland zelden uitgevoerd.

FOLLOW UP MAAG TRANSPOSITIE VERSUS JEJUNUM INTERPONAAT

In **hoofdstuk 3** beschrijven we de korte- en middellange termijn resultaten van MT versus JI. Onze gegevens toonden geen mortaliteit, maar wel significante morbiditeit na beide procedures. Anastomotische complicaties zoals lekkage, stenose en functionele obstructie werden significant vaker gerapporteerd na JI. Tijdens de follow-up (mediane leeftijd 14 jaar) werden gastro-intestinale klachten gerapporteerd door de meeste patiënten na beide procedures. Er leek echter een tendens te zijn tot een hoger percentage refluxklachten na MT. We vonden bovendien dat patiënten na JI orale voeding beter leken te verdragen dan MT-patiënten. Tevens was bij 44% van de GPU-patiënten het gewicht voor de leeftijd lager dan - 2SD vergeleken met slechts 26% van de JI-patiënten.

We concluderen daarom dat MT en JI beide OV-technieken zijn met significante morbiditeit. JI lijkt meer korte termijn complicaties te hebben, terwijl MT meer morbiditeit liet zien gedurende de follow-up.

RESPIRATOIRE MORBIDITEIT

Hoofdstuk 4 richt zich op de respiratoire gevolgen van MT en JI. Deze studie laat zien dat luchtwegklachten zoals hoesten en dyspnoe voorkwamen bij de meerderheid van de patiënten na beide procedures. Echter, astma-achtige symptomen en dyspnoe bij inspanning leken vaker voor te komen na MT. Longfunctietesten toonden zowel na MT als JI een verslechtering in vergelijking met een gezonde controlegroep. De longfunctieparameters bij JI-patiënten lagen echter dichter bij de waardes van de controlegroep dan bij MT-patiënten. Patiënten na MT vertoonden een afname van de totale longcapaciteit (TLC) in vergelijking met JI-patiënten, met voornamelijk een restrictief respiratoir beeld. Dit kan te maken hebben met de aanwezigheid van het ruimte-innemende orgaan in de borstkas, die de normale longontwikkeling kan beïnvloeden4. Het kan ook veroorzaakt zijn door schade aan de longen als gevolg van langdurige blootstelling van long parenchym aan maagreflux[5], aangezien refluxsymptomen aanwezig waren bij de meeste MT-patiënten (**hoofdstuk 5**). We concluderen dat respiratoire klachten en verminderde longfunctie erger zijn na MT dan na JI. Respiratoire follow-up op volwassen leeftijd is daarom belangrijk.

VERANDERINGEN VAN HET INTERPONAAT

Behalve dat effecten op het respiratoire systeem kunnen optreden, kan OV chirurgie ook het gastro-intestinale systeem beïnvloeden. Zowel veranderingen in (patho-)fysiologie als op cellulair niveau kunnen voorkomen. Verhoogd risico op Barrett's oesophagus en zelfs zeldzame gevallen van slokdarmcarcinoom bij OA-patiënten zijn in de literatuur beschreven[6-7]. In **hoofdstuk 5** werden daarom de langetermijneffecten op de gastro-intestinale functie en anatomische en mucosale veranderingen onderzocht bij volwassenen na MT en JI. De studie bestaat uit semi-gestructureerde interviews, contraststudies en endoscopie met histopathologie. Het doel was om na te gaan of er in de loop van de tijd significante veranderingen van de natieve slokdarm en het interponaat optraden.

Uit onze analyse blijkt dat de meerderheid van de MT-patiënten refluxklachten had. De JI-patiënten hadden minder refluxsymptomen, maar meer dysfagie. Ook was er sprake van dilatatie van de JI-transplantaten. Ondanks de dysfagie en de gedilateerde JI-transplantaten verdroegen alle JI-patiënten volledige orale voeding. Bij 22% van de MT-patiënten werd intestinale metaplasie gevonden. Het belang van deze bevinding is onduidelijk en of dit in de toekomst zou kunnen leiden tot Barrett's oesophagus is niet bekend. In ieder geval waren deze histologische veranderingen niet geassocieerd met refluxsymptomen. Daarom kunnen refluxsymptomen niet worden gebruikt als een betrouwbare detector van mucosale veranderingen. We concluderen dat klinische en endoscopische surveillance voor LGEA-patiënten belangrijk is, vooral na MT. Verder is van belang dat een derde van de MT-patiënten nog steeds ondergewicht had, zoals ook beschreven in **hoofdstuk 2**. JI-patiënten lieten daarentegen een gewichtstoename zien in de tijd.

KWALITEIT VAN LEVEN

Naast de somatische klachten is het relevant om ook de psychosociale status van de patiënten in kaart te brengen. Lange termijn morbiditeit na OV chirurgie voor LGOA is significant. De vraag is of dit in het dagelijks leven tot een afname kan leiden van de kwaliteit van leven (KvL). Slechts een paar studies hebben KvL na MT onderzocht en meestal zonder gevalideerde vragenlijst[8]. Bovendien KvL na JI is nog nooit eerder geanalyseerd. In **hoofdstuk 6** hebben we (gezondheidsgerelateerde) KvL onderzocht met behulp van GIQLI, CHF87-BREF, WHOQOL-BREF en TNO AZL TACQoL/TAAQoL. We vonden dat generieke en ziekte-specifieke KvL bij de meerderheid van de patiënten na OV vergelijkbaar was met gezonde controles. We vonden bovendien geen verschil in KvL tussen MT- en JI-patiënten. In beide groepen waren postoperatieve morbiditeit en re-interventie niet geassocieerd met een verslechtering in KvL.

Deze bevindingen suggereren dat lichamelijke klachten na OV geen gevolgen hebben op de perceptie van het welzijn van deze patiënten. Een mogelijke verklaring kan zijn dat patiënten en hun families efficiënte coping strategieën hebben ontwikkeld.

NIEUWE OESOPHAGUS-SPARENDE STRATEGIE

Dit proefschrift en de eerste zes hoofdstukken focussen op de twee OV-procedures die door de INoEA worden aanbevolen voor LGOA[1]. Onlangs wees de INoEA er echter op dat alles gedaan moet worden om de natieve slokdarm van de patiënt te behouden en dat OR-technieken alleen mogen worden gebruikt wanneer primaire anastomosering niet mogelijk is. Primair herstel van de continuïteit van de oesophagus kan worden bereikt door middel van een "*delayed*" primaire anastomose of door tractietechnieken. De eerste wordt twee tot drie maanden na de geboorte uitgevoerd. Los van de bijbehorende langdurige ziekenhuisopname kan dit leiden tot slikproblemen als gevolg van de uitgestelde introductie van orale voeding en tot ademhalingsproblemen ten gevolge van aspiratie[9]. Toekomstige strategieën voor LGOA zijn tractietechnieken die de natieve slokdarm behouden en die uitgevoerd kunnen worden binnen enkele dagen na de geboorte. In **hoofdstuk 7** beschrijven we de resultaten van de eerste cohortstudie van LGOA-patiënten behandeld met TTT. In deze studie hebben we ons gericht op veiligheid, haalbaarheid en efficiëntie van de procedure. Acht van de tien kinderen ondergingen met succes TTT en na vier

tot zes dagen tractie kon een thoracoscopische primaire anastomose worden gelegd. Bij twee kinderen mislukte de procedure, waarna respectievelijk GPU en JI werden uitgevoerd. Als gevolg van de tractie wordt de gastro-oesofageale overgang uitgerekt en naar craniaal getrokken in de thorax, waardoor alle antirefluxmechanismen ongedaan worden gemaakt. Daarom wordt vier tot zes weken na het uitvoeren van de primaire anastomose antirefluxchirurgie verricht in de vorm van laparoscopische fundoplicatie. We concluderen dat TTT een haalbare en veilige natieve oesofagus -sparende procedure is voor de behandeling van LGEA. Tractie kan bovendien direct na de geboorte worden uitgevoerd, zonder gastrostomie, en leidt tot een beperkte opnameduur.

DISCUSSIE

In dit proefschrift konden we niet één van de OV procedures aanwijzen als optimale techniek. We hebben echter bepaalde tendensen kunnen identificeren die van belang zijn. JI lijkt geassocieerd met meer postoperatieve morbiditeit op korte termijn, zoals naadlekkage, stenose en functionele obstructie. Een reden hiervoor kan de zeer precaire bloedvoorziening van het JI-interponaat zijn. Dit kan leiden tot ischemie van de anastomose. Niet veel chirurgen hebben de expertise om deze procedure uit te voeren en daarom is er een gebrek aan studies over deze techniek en variëren de resultaten tussen diverse centra. Ondanks de korte termijn morbiditeit, is de lange termijn uitkomst van JI met betrekking tot voeding, groei en gastro-intestinale- en luchtwegklachten gunstiger in vergelijking met MT.

Hoewel MT minder korte termijn complicaties lijkt te hebben, leidt gastro-oesofageale reflux op de lange duur tot aandoeningen van de luchtwegen en van het maag-darmkanaal. Intestinale metaplasie wordt gevonden in 22% van de GPU. Het is niet duidelijk of deze bevinding zal leiden tot Barrett's oesophagus of uiteindelijk zelfs tot het ontwikkelen van een carcinoom. Endoscopische surveillance van patiënten met primair herstel van OA wordt aanbevolen volgens de richtlijnen van de European en North American Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPHGAN/NASPHGAN). Wij zijn van mening dat een nog intensiever surveillanceprogramma geïndiceerd zou zijn voor patiënten na MT, gezien de hoge prevalentie van gastro-oesofageale reflux.

MT-patiënten ontwikkelen meer respiratoire symptomen tijdens de follow-up. Dit komt deels door aanhoudende reflux, deels door de aanwezigheid van een ruimte-innemend orgaan in de thorax. Tracheomalacie kan ook een belangrijke rol spelen, zoals bij alle OA-patiënten

De respiratoire en gastro-intestinale morbiditeit na OV lijkt geen invloed te hebben op KvL bij deze patiënten. Patiënten hebben efficiënte coping strategieën ontwikkeld en/of zijn gewend geraakt aan de klachten. Dit werd ook gevonden bij kinderen met een chronische ziekte in eerdere studies[10].

Hoewel OV voor LGOA een haalbare techniek is, moet het trachten te behouden van de natieve slokdarm worden gezien als de eerste stap in de behandeling van LGEA[1]. De oesophagus sparende procedure TTT komt naar voren als een veelbelovende nieuwe techniek. Echter, deze wordt alleen uitgevoerd in hoog-expertisecentra. Daarom zijn er beperkt data beschikbaar wat vergelijking moeilijk maakt. Pilotgegevens laten echter zien dat naadlekkage, stenose en reflux optreden na TTT, zoals ook beschreven na OV. Naarmate TTT steeds meer wordt uitgevoerd, zullen er meer lange termijn gegevens beschikbaar komen. Hopelijk zullen toekomstige goed opgezette onderzoeken bewijs leveren voor de beste chirurgische benadering voor LGOA-correctie. Centralisatie van de zorg en samenwerking tussen de Centers of Expertise lijkt ons cruciaal in dit proces.

REFERENTIES

1 van der Zee DC, Bagolan P, Faure C, Gottrand F, Jennings R, Laberge JM, et al. Position paper of INoEA working group on long-gap esophageal atresia: for better care. Front Pediatr 2017;5:2– 4. doi: 10.3389/fped.2017.0 0 063 .

2 Bax KM. Jejunum for bridging long-gap esophageal atresia. Semin Pediatr Surg 2009;18(1):34–39Cauchi

3 JA, Buick RG, Gornall P, SimmsMH, Parikh DH. Oesophageal substitutionwith free and pedicled jejunum: short- and long-term outcomes. Pediatr Surg Int 2007;23(1):11–19

4 Friedrich L, Pitrez PM, Stein RT, et al. Growth rate of lung function in healthy preterminfants. Am J Respir Crit Care Med 2007;176:1269–73.

5 Schachter L, Dixon J, Pierce R, et al. Severe gastroesophageal reflux is associated with reduced carbon monoxide diffusing capacity. Chest 2003;123(6):1932–8.

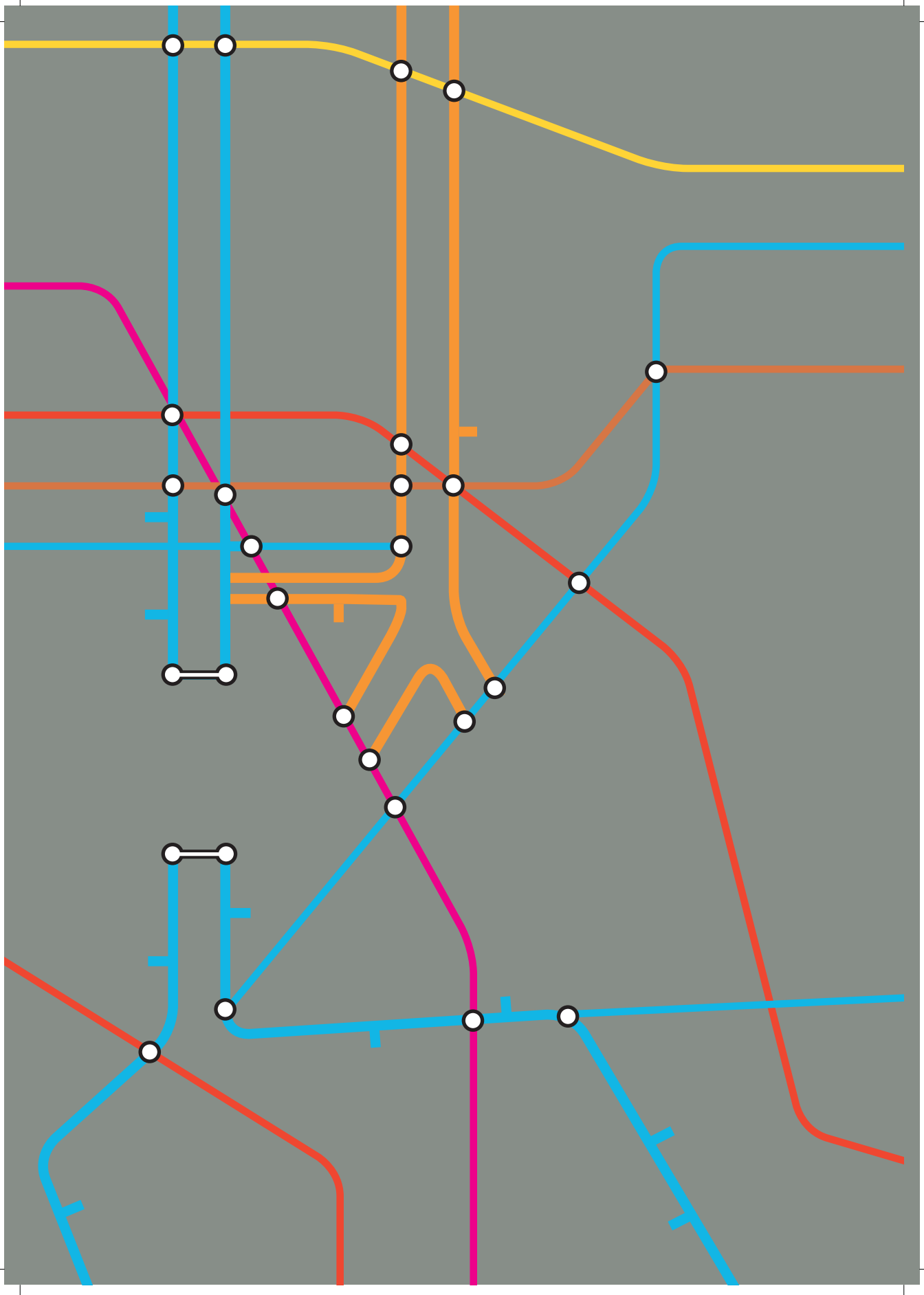
6 Vergouwe FWT, IJsselstijn H, Biermann K, Erler NS, Wijnen RMH, Bruno MJ, Spaander MCW. High Prevalence of Barrett's Esophagus and Esophageal Squamous Cell Carcinoma After Repair of Esophageal Atresia. Clin Gastroenterol Hepatol 2018; 16: 513-521.e6. [DOI: 10.1016/J.CGH.2017.11.008]

7 PultrumBB,BijleveldCM,DeLangenZJ,PlukkerJTM.Developmentofanadenocarcinomaofthe esophagus 22 years after primary repair of a congenital atresia. J Pediatr Surg (e-pub ahead of print 2005; doi:10.1016/j.jpedsurg.2005.08.042).

8 S.P. Tan Tanny, et al., Quality of life assessment in esophageal atresia patients: a systematic review focusing on long-gap esophageal. J Pediatr Surgery, Available online 5 October 2019, https://doi.org/10.1016/j.jpedsurg.2019.08.040

9 van Tuyll van Serooskerken ES, Lindeboom MYA, Verweij JW Childhood outcome after correction of long-gap esophageal atresia by thoracoscopic external traction technique. J Pediatr Surg 2021 Oct;56(10):1745-1751. doi: 10.1016/j.jpedsurg.2021.05.001

10 Meijer, et al. Social functioning in children with a chronic illness. J Child Psychol Psychiatry. 2000;41(3):309–17.



APPENDICES

List of publications
About the author
Dankwoord

LIST OF PUBLICATIONS

Gabriele Gallo, Sander Zwaveling, Henk Groen, David Van der Zee, Jan Hulscher.
Long-Gap Esophageal Atresia: a Meta-Analysis of Jejunal Interposition, Colon Interposition, and Gastric Pull-Up.
European Journal of Pediatric Surgery 2012

Gabriele Gallo, Sander Zwaveling, David C. Van der Zee, Klaas N. Bax ,Zacharias J. de Langen, Jan B.F. Hulscher.
A two-center comparative study of gastric pull-up and jejunal interposition for long-gap esophageal atresia.
Journal of Pediatric Surgery 2015

Gabriele Gallo, Elianne J.L.E. Vrijlandt, Hubertus G.M. Arets, Gerard H. Koppelman, David C. Van der Zee, Jan B.F. Hulscher, Sander Zwaveling.
Respiratory function after esophageal replacement in children.
Journal of Pediatric Surgery 2017

Eleonora S van Tuyll van Serooskerken, Gabriele Gallo, Bas LAM Weusten, Jessie Westerhof, Lodewijk AA Brosens, Sander Zwaveling, Johannes W Verweij, Jan BF Hulscher, Hubertus G.M. Arets, Arnold J.N. Bittermann, David C van der Zee, Stefaan HAJ Tytgat*, Maud YA Lindeboom*.
Graft dilatation and Barrett's esophagus in adults after esophageal replacement in long-gap esophageal atresia.
Submitted

Gabriele Gallo, E.S. van Tuyll van Serooskerken, S.H.A.J. Tytgat, D.C. van der Zee, C.M.G. Keyzer-Dekker,S. Zwaveling, J.B.F. Hulscher, H. Groen, M.Y.A. Lindeboom.
Quality of life after esophageal replacement in children.
Journal of Pediatric Surgery 2021

David C. van der Zee, Gabriele Gallo, Stefaan H. A. Tytgat.
Thoracoscopic traction technique in long-gap esophageal atresia: entering a new era.
Surgical Endoscopy 2015

**Shared last author*

ABOUT THE AUTHOR

Gabriele Gallo werd op 11 April 1986 in Avellino (Italië) geboren. Hij groeide op in Toscane en later in Rome met zijn broer Mario. Hij doorliep tot 2004 het gymnasium Liceo Scientifico Talete te Rome. Aangezien zijn ouders en broer rechten hadden gestudeerd leek het Gabriele een goed idee om geneeskunde te gaan studeren. Dat deed hij aan de Katholieke Universiteit van Rome (Policlinico A. Gemelli). Tijdens zijn master voltooide hij een onderzoeksstage in het UMCG bij de afdeling Kinderchirurgie onder leiding van prof. dr. Jan Hulscher (2009), dit resulteerde later in hoofdstuk 3 van dit proefschrift. Tijdens deze stage ontwikkelde hij een passie voor het leven in Nederland en tevens voor stroopwafels. Wat de opleiding Heelkunde in Nederland kon bieden bleek voor hem een openbaring. Daarom besloot hij na het afronden van zijn studie geneeskunde naar Groningen te emigreren. Dit deed hij om toe te werken naar een kans om in opleiding tot chirurg te komen. Om dit doel te realiseren bouwde hij klinische werkervaring op, eerst als ANIOS Intensive Care in het UMCG, later als ANIOS chirurgie in het UMCG en in het Martini Ziekenhuis. In 2016 startte hij met de opleiding Heelkunde in het Martini Ziekenhuis onder leiding van dr. W. Kelder. Momenteel is hij zich aan het differentiëren in de Kinderchirurgie in het UMCG (opleider: dr. R.J. van Ginkel en dr J.F.M. Lange).

DANKWOORD

Het eerste artikel van dit project dateert uit 2012, toen is ook daadwerkelijk mijn avontuur in Nederland begonnen. Het begon zonder zekerheden, maar met veel passie en nieuwsgierigheid. Ik heb het privilege gehad (en misschien ook het geluk) om mensen tegen te komen die me geïnspireerd hebben en die me vertrouwen hebben gegeven. Dat heeft mij de kans gegeven mijn motivatie om te zetten in persoonlijke groei en ontwikkeling van mijn carrière. Het is niet in woorden te vatten hoe dankbaar ik ben voor de steun die ik vanaf het begin heb gekregen maar toch wil ik het proberen.

Beste **prof. dr. M.Y.A. Lindeboom**, beste Maud, zonder jouw vertrouwen en steun zou dit project niet mogelijk zijn geweest. Jouw kritische blik en je aandacht voor details zijn essentieel geweest. Dit zijn aspecten die ik met me mee zal nemen bij het doen van onderzoek in de toekomst. We hebben memorabele momenten doorgebracht samen. Dan denk ik bijvoorbeeld aan het pizza-overleg in het WKZ en de gesprekken onder de zon van Barcelona tijdens het ESPES congres. Ik hoop dat er nog vele zullen volgen. Ook bedankt voor de mogelijkheid om wereldwijde experts op het gebied van oesofagus atresie te mogen ontmoeten en meningen met hen uit te wisselen.

Beste **prof. dr. J.B.F. Hulscher**, beste Jan, ik houd het kort, je hebt me geïnspireerd tijdens het hele traject. Vanaf het begin ben ik gefascineerd geweest door de manier waarop je praatte over onderzoek. Begeleiding door een briljant persoon als jou geeft aan iedereen, die sterk gemotiveerd is, de mogelijkheid om resultaten te bereiken. Jan, ik ken niet genoeg Nederlandse woorden om je te bedanken.

Beste **dr. S. Zwaveling**, beste Sander, ik heb je leren kennen zonder baard en ik herinner me met veel plezier onze dagen in het WKZ aan het begin van dit project. Bedankt voor de fundamentele bijdrage die je hebt geleverd aan dit proefschrift. Ik waardeer je capaciteit om verder te kijken dan de woorden, recht naar het hart van de kwestie.

Beste **dr. S. Tytgat**, beste Stefaan, met dank aan jou heb ik kunnen deelnemen aan mijn eerste thorascopische correctie van long-gap oesofagus atresie in Utrecht. Jouw enthousiasme is aanstekelijk, niet alleen in de operatiekamer, maar in het algemeen als je over je werk praat. Verder waardeer ik jouw commentaar op onze artikelen erg. Je schreef dit uit op papier in plaats van digitaal. Ik heb dit altijd ervaren als een heel romantisch idee van de wetenschap en ons werk.

Beste **prof. dr. D.C van der Zee**, beste David, bij deze wil ik je hartelijk bedanken voor de mogelijkheid die jij mij hebt geboden om in Utrecht te promoveren. Vanaf het begin heb ik je sensibiliteit en je optimisme gewaardeerd. Je hebt het vertrouwen op me overgebracht dat dit proefschrift mogelijk was.

Dank aan alle leden van de leescommissie **prof. dr. M.N. Bekke**, **prof. dr. E.M. van de Putte**, **prof. dr. M.C.W. Spaander**, **prof. dr. C.M. Bilardo** en **dr. S.W.J. Terheggen-Lagro** voor het lezen en beoordelen van mijn proefschrift. Als jullie naar Rome op vakantie gaan, dan weten jullie mij te vinden voor tips.

Sofie van Tuyll, de eerste dag dat we samen werkten, speelden we een potje tafeltennis in het WKZ. Een prachtig begin zou ik zeggen! Bedankt voor je hulp en je geduld bij de projecten, waar we samen aan deel genomen hebben. Ik bewonder je analytische capaciteiten en schrijfvaardigheid erg en ik neem ze als voorbeeld.

Claudia Keyzer-Dekker, bedankt voor de mooie momenten die we hebben doorgebracht in het UMCG en voor je cruciale bijdrage aan de ontwikkeling van de studie over de kwaliteit van leven na oesofagus vervangende chirurgie. Zoals je kan zien in de stellingen, waardeer ik je visie op de prioriteiten in het leven erg.

Henk Groen, zonder jou zou ik een schipbreukeling zijn geweest, verloren in de zee van de statistiek. Je bent mijn anker en ik hoop dat we zullen blijven samenwerken in de toekomst.

Stafleden Kinderchirurgie UMCG, het is een privilege te zijn opgeleid door jullie. Nooit heb ik twijfels gehad dat dit is wat ik het liefste wilde. Het is een droom die uitkomt en ik zal mijn best doen jullie niet teleur te stellen.

Zacharias De Langen, tijdens mijn allereerste onderzoeksstage heb ik jou leren kennen. Je bent mijn voorbeeld van positiviteit en optimisme in het leven. We zijn alle samen begonnen en ik voel me gelukkig deze dag ook met jou te delen. Wat leuk dat jij ook in de Turftorenstraat hebt gewoond! Ik kijk altijd naar no. 7 als ik daar langs fiets.

Maarten Schurink, we hebben geen gemeenschappelijke artikelen. Maar hoe kan ik onze gezamenlijke momenten vergeten? Zowel tijdens mijn eerste klinische ervaring als ANIOS als tijdens diners en congressen. Ik hoop nog veel rooftop aperitieven met je te beleven.

Beste **dr. W.Kelder** en de hele **Maatschap Chirurgen Martini Ziekenhuis** ik wil jullie bedanken voor het voorrecht door jullie opgeleid te zijn. Ik heb de mogelijkheid gehad parallel te werken aan mijn opleiding en mijn promotie. We hebben onuitwisbare momenten doorgebracht ,die ik de rest van mijn leven met mee zal dragen en die me een beter persoon hebben gemaakt. Ik keer graag af en toe terug voor een borrel in het chirurgencafé.

Opleider van regio VI **dr. R.J.van Ginkel**, ik ben heel blij dat jij voor de eerste keer een Italiaan hebt aangenomen in je regio (misschien in Nederland?), bedankt voor jouw vertrouwen in mij. Onze openhartige gesprekken over mijn privéleven zijn waardevol.

Bas Wallis de Vries, ik zal je altijd dankbaar zijn, dat je me de kans hebt gegeven om te beginnen als ANIOS in het UMCG, zonder die eerste stap zou ik dit traject nooit hebben kunnen starten. Gelukkig heb ik de taaltest gehaald!

Jaap Tulleken en **Jacqueline Koeze**, toen ik ben begonnen bij jullie op de Intensive Care, was mijn Nederlands nog verre van perfect en mijn klinische capaciteiten waren slecht, maar ik had veel zin om te leren. Jullie hebben me in de gelegenheid gesteld dit prachtige avontuur voort te zetten. Overdag werken en Nederlandse les volgen in de avond was uitdagend, maar als ik eraan terugdenk heb ik het met immens plezier gedaan, met name dankzij jullie. Jullie hebben me in de gelegenheid gesteld dit prachtige avontuur voort te zetten.

Een speciaal dankwoord aan alle **AIOS chirurgie** van de **regio VI**, samen hebben we niet alleen hard gewerkt als een team maar we hebben ook geweldige momenten doorgebracht zoals de chirurgencup, skiweekend, borrels, party's, congressen enz.

Grazie ai miei paraninfi, in particolare a **Fabrizio Bianchi** che per la prima volta mi ha aperto la porta della international student house dove abbiamo vissuto nel 2009. Possiamo veramente dire che questa avventura è iniziata (dopo tanti Coliandro e Kenshiro) e continua insieme.

Grazie a tutti gli amici della gabbia di matti che nel corso degli anni hanno reso Groningen un posto bellissimo e che usano *f.mecozzi@rug.nl* per connettersi ai wifi pubblici. **Kaps™**, **Mec™**, **Presidont™**, **Fede Font** sono estasiato all'idea di poter trascorrere ancora tante avventure con voi, il segreto è sempre quello. E poi Don Ciccio de la Vega, Paolini, Storm, Demps, Sasà, iTeto, David, Michi, Juma, la Stot, Mixana, Beppe Caroli, il coach, Marchitiello, Alessandra Olimpia, MDL, il commissario, Carmen e gli inquilini di Prinsesseweg 37a en Friesestraatweg 113. Grazie di cuore a **Bernard Specken**, il più italiano dei miei amici olandesi.

Infine grazie ai miei genitori che mi hanno supportato in ogni mia scelta e grazie a tutto il resto della mia chiassosa famiglia per le estati e i Natali bellissimi che trascorriamo assieme. Grazie a Mario, Cecilia ed Alessandro. Alessandro tra qualche anno sarai in grado di comprendere queste poche righe e leggerai quanto ti voglio bene.

Groningen, november 2022,

Gabriele