DESIGN DATBureau, www.datbureau.nl.
PRINTED ProefschriftMaken, www.proefschriftmaken.nl.

The work presented in this thesis was conducted at the Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center Rotterdam, The Netherlands and at the Department of Pediatric Surgery, Erasmus MC University Medical Center Rotterdam – Sophia Children's Hospital, The Netherlands.

ISBN/EAN: 978-94-6380-762-3

Financial support for printing this thesis was kindly provided by:
- Department of Gastroenterology and Hepatology of Erasmus MC University Medical Center Rotterdam
- Department of Pediatric Surgery of Erasmus MC University Medical Center – Sophia Children's Hospital Rotterdam
- Erasmus University Rotterdam
- Dr. Falk Pharma Benelux B.V.
- Chipsoft
- Nederlandse Vereniging voor Gastroenterologie
- Norgine

Long-term Follow-up After Esophageal Atresia Repair
Gastrointestinal morbidity in children and adults

Lange termijn follow-up na herstellen van slokdarmatresie
Maagdarmproblemen in kinderen en volwassenen

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus,

prof. dr. R.C.M.E. Engels

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op
woensdag 28 oktober 2020 om 15.30 uur door

Florence Wilhelmina Theresia (Floor) Vergouwe

geboren te Amsterdam

Erasmus University Rotterdam

Promotiecommissie

Promotoren
Prof. dr. M.J. Bruno
Prof. dr. R.M.H. Wijnen

Overige leden
Prof. dr. M.P. Peppelenbosch
Prof. dr. R.H.J. Houwen
Prof. dr. J.C. Escher

Copromotoren
Prof. dr. M.C.W. Spaander
Dr. H. IJsselstijn

Paranimfen
M.J.H. van Campenhout
R.M. Blom

1

General introduction and outline of the thesis

Esophageal atresia

Esophageal atresia (EA) with or without tracheoesophageal fistula (TEF) is a relatively common congenital anomaly involving the esophagus and trachea. It is the most common congenital anomaly of the esophagus, which was first described in twins by Durston in 1670 [1]. In Europe, one in 4,000 newborns is born with EA [2]. In the Netherlands each year around 35-55 newborns are born with EA [3].

The Gross classification distinguishes five types of EA based on the presence and location of atresia and TEF: isolated EA (type A), EA with proximal TEF (type B), EA with distal TEF (type C), EA with dual TEF's (type D), and isolated TEF (type E) FIGURE 1.1 [4]. EA type C (EA with a distal TEF) is the most common form (85.8%), followed by type A (7.8%), E (4%), D (1.4%) and B (0.8%) [4].

Early surgical intervention is needed as EA results in a collection of saliva in the blind proximal esophageal pouch, causing regurgitation, coughing and choking. In types B to D – depending on the location of a coexisting TEF – food, saliva or acid stomach contents passes through the fistula into the trachea and lungs, inducing respiratory problems, aspiration pneumonia or even acute upper respiratory tract obstruction with a subsequent respiratory arrest.

Surgery and survival

In 1939, Ladd and Leven performed the first successful surgical corrections of EA [5, 6]. These first two long-term survivors of EA underwent staged repair with delayed esophageal replacement: an antethoracic skin-tube conduit of the thoracic esophagus and a jejunal interposition. The first successful primary repair (end-to-end anastomosis) of EA was performed by Haight in 1941 [7]. In the following decades the survival of children born with EA showed spectacular improvement FIGURE 1.2 [8, 9]. Nowadays, with improvement of surgical techniques and intensive care treatments, survival after EA repair is approaching 95%-100% in dedicated centers. Only children with extensive comorbidity – due to severe prematurity, major other congenital abnormalities or chromosomal defects – die [10, 11].

As the majority of children survives surgical correction of EA beyond the neonatal period, focus has shifted from short-term mortality to long-term morbidity. EA is no longer a medical problem in just young infants, but a lifelong problem in all patients born with EA. Besides direct disease related gastrointestinal and respiratory morbidity, growth impairment and neurodevelopmental problems are frequently seen in EA patients [12-14]. A multidisciplinary approach to morbidity in EA patients is necessary as most of these problems are multi-factorial. A structured follow-up may help to reduce overall morbidity and improve quality of life of children with EA and their families [15].

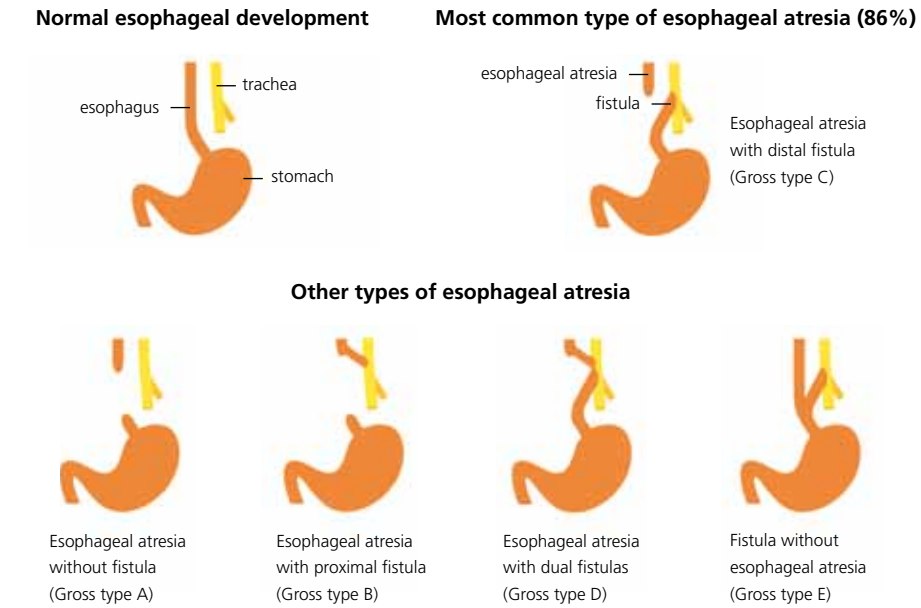


Figure 1.1 Normal esophageal development and the five types of esophageal atresia (Gross types A, B, C, D and E).

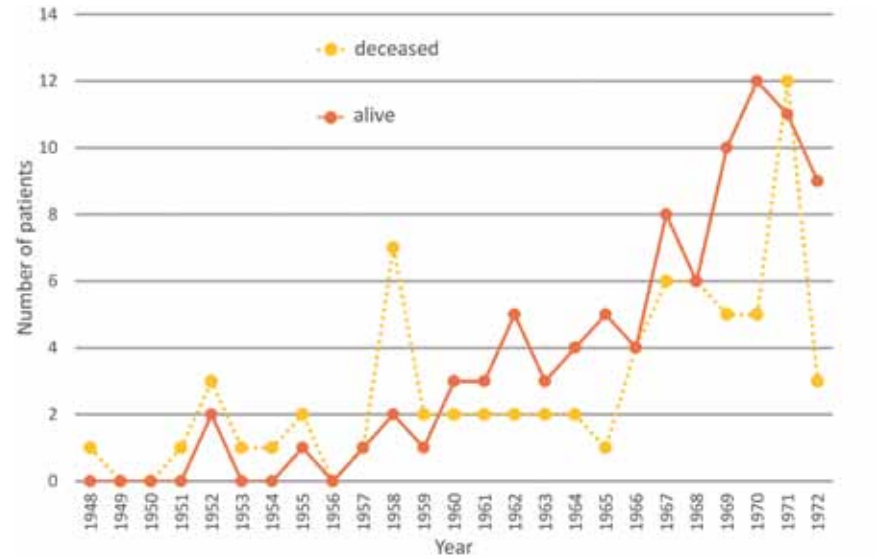


Figure 1.2 Children born with EA and treated between 1948 and 1972 in the Erasmus MC-Sophia Children's Hospital in Rotterdam (Figure adapted from EUR thesis van Walleghem 1973).

Aims and outline of the thesis

This thesis aims to optimize long-term gastrointestinal follow-up of EA patients.

As described above, many EA patients – both children and adults – experience GER. GER results in gastrointestinal problems such as dysphagia, feeding difficulties, esophageal strictures, esophagitis, BE, and esophageal cancer. Since gastrointestinal and pulmonary problems can compromise growth, this thesis will start with a longitudinal evaluation of growth of EA patients from infancy up to school age in chapter 2. In addition, this chapter focuses on determinants associated with growth impairment.

Chapter 3 gives an overview of the prevalence of esophagitis, BE, and esophageal cancer in EA patients. The few strategies for esophageal surveillance programs suggested in literature are shortly mentioned in this chapter.

At present, it is recommended to monitor GER at time of discontinuation of acid suppression and during long-term follow-up in symptomatic children born with EA. The results of routine evaluation of GER in EA patients aged ≤18 months and 8-years old using combined impedance and pH monitoring are evaluated in chapter 4.

Chapter 5 describes the incidence of refractory strictures of the esophageal anastomosis in a large national multicenter cohort of children born with EA. Determinants of refractory stricture formation are discussed in more detail in this chapter.

GER can result in chronic damage to esophageal mucosa. Chapter 6 assesses the prevalence of BE and esophageal carcinoma in a prospective screening and surveillance program in adult EA patients.

Four EA patients that developed carcinoma in the gastrointestinal tract at a relatively young age are described in more detail in chapter 7.

In chapter 8 the main findings and conclusions of the studies are placed in broader perspective and suggestions for future research are discussed.

Finally, in chapter 9 the results of all studies are summarized (English and Dutch).

REFERENCES

1 Durston, W., *A narrative of a monstrous birth in Plymouth, Octob. 22 1670: together with the anatomical observations taken thereupon*. Philos Trans R Soc Lond 1670. **V**: p. 2096-7.

2 *EUROCAT Prevalence Tables (1980-2015)*. [cited 2017 August 24, 2017]; Available from: http://www.eurocat-network.eu/accessprevalencedata/prevalencetables

3 Schönbeck, Y., et al., *Aangeboren afwijkingen in Nederland 2001-2013: Gebaseerd op de landelijke perinatale registraties*. 2015, TNO: Leiden.

4 Gross, R.E., *The Surgery of Infancy and Childhood*. Philadelphia: W. B. Saunders Company, 1953: p. 441-444.

5 Ladd, W.E., *The surgical treatment of esophageal atresia and tracheoesophageal fistulas*. N Engl J Med, 1944. **230**: p. 625-637.

6 Leven, N.L., *Congenital atresia of the esophagus with tracheoesophageal fistula*. Thorac Cardiovasc Surg, 1941. **10**: p. 48-657.

7 Haight, C. and H. Towsley, *Congenital atresia of the esophagus with tracheoesophageal fistula: extrapleural ligation of fistula and end-to-end anastomosis of esophageal segments*. Surg Gynecol Obstet, 1943(76): p. 672-688.

8 van Walleghem, J.K.R.A.C., *Oesophagusatresie*. 1973, Erasmus University Rotterdam.

9 Spitz, L., et al., *Oesophageal atresia: at-risk groups for the 1990s*. J Pediatr Surg, 1994. **29**(6): p. 723-5.

10 Wang, B., et al., *A nationwide analysis of clinical outcomes among newborns with esophageal atresia and tracheoesophageal fistulas in the United States*. J Surg Res, 2014. **190**(2): p. 604-12.

11 Sulkowski, J.P., et al., *Morbidity and mortality in patients with esophageal atresia*. Surgery, 2014. **156**(2): p. 483-91.

12 Gottrand, M., et al., *Motility, digestive and nutritional problems in Esophageal Atresia*. Paediatr Respir Rev, 2016. **19**: p. 28-33.

13 Sadreameli, S.C. and S.A. McGrath-Morrow, *Respiratory Care of Infants and Children with Congenital Tracheo-Oesophageal Fistula and Oesophageal Atresia*. Paediatr Respir Rev, 2016. **17**: p. 16-23.

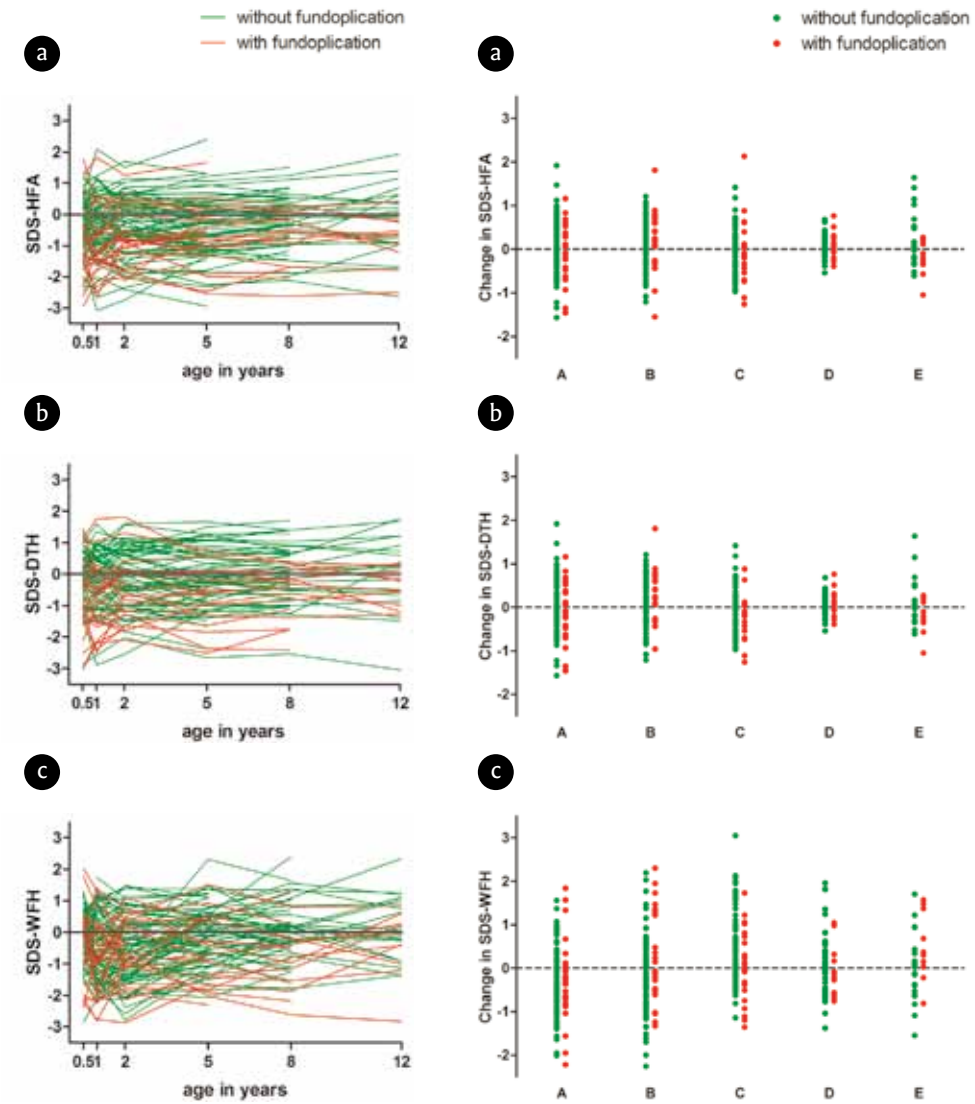
14 IJsselstijn, H., et al., *Growth and development after oesophageal atresia surgery: Need for long-term multidisciplinary follow-up*. Paediatr Respir Rev, 2016. **19**: p. 34-8.

15 IJsselstijn, H., et al., *Assessment and significance of long-term outcomes in pediatric surgery*. Semin Pediatr Surg, 2017. **26**(5): p. 281-285.

16 Gischler, S.J., et al., *Interdisciplinary structural follow-up of surgical newborns: a prospective evaluation*. J Pediatr Surg, 2009. **44**(7): p. 1382-9.

17 IJsselstijn, H., N.W. van Beelen, and R.M. Wijnen, *Esophageal atresia: long-term morbidities in adolescence and adulthood*. Dis Esophagus, 2013. **26**(4): p. 417-21.

18 Felix, J., *Aetiological Studies in Oesophageal Atresia/Tracheo-Oesophageal Fistula: a combined genetic and environmental approach*. 2007.



Supplementary figure 2.1
Individual trajectories for SDS-HFA (a), SDS-DTH (b) and SDS-WFH (c) plotted against assessment age (patients without a fundoplication in green, patients with a fundoplication in red).

Supplementary figure 2.2
Change in SDS-HFA (a), SDS-DTH (b) and SDS-WFH (c) in children with (red) and without (green) fundoplication surgery between two successive visits:
A= change between 0.5-1 years;
B= change between 1-2 years,
C= change between 2-5 years,
D= change between 5-8 years;
E= change between 8-12 years.

3

Screening and surveillance in esophageal atresia patients: current knowledge and future perspectives

Eur J Pediatr Surg. 2015 Aug;25(4):345-52

Floor W.T. Vergouwe, Hanneke IJsselstijn, René M.H. Wijnen,
Marco J. Bruno, Manon C.W. Spaander

7

Four cancer cases after esophageal atresia repair: Time to start screening the upper gastrointestinal tract

World J Gastroenterol. 2018 Mar 7;24(9):1056-1062

Floor W.T. Vergouwe, Madeleine Gottrand, Bas P.L. Wijnhoven, Hanneke IJsselstijn, Guillaume Piessen, Marco J. Bruno, René M.H. Wijnen, Manon C.W. Spaander

ABSTRACT

Esophageal atresia (EA) is one of the most common congenital digestive malformations and requires surgical correction early in life. Dedicated centers have reported survival rates up to 95%. The most frequent comorbidities after EA repair are dysphagia (72%) and gastroesophageal reflux (GER) (67%). Chronic GER after EA repair might lead to mucosal damage, esophageal stricturing, Barrett's esophagus and eventually esophageal adenocarcinoma. Several long-term follow-up studies found an increased risk of Barrett's esophagus and esophageal carcinoma in EA patients, both at a relatively young age. Given these findings, the recent ESPGHAN-NASPGHAN guideline recommends routine endoscopy in adults born with EA. We report a series of four EA patients who developed a carcinoma of the gastrointestinal tract: three esophageal carcinoma and one colorectal carcinoma in a colonic interposition. These cases emphasize the importance of lifelong screening of the upper gastrointestinal tract in EA patients.

INTRODUCTION

With a prevalence of 2.43 per 10,000 births, esophageal atresia (EA) with or without a tracheoesophageal fistula (TEF) is one of the most common congenital digestive malformations [1]. Surgical correction needs to be performed shortly after birth. Due to advanced surgical techniques and improved perioperative care, survival rate has increased up to 95% in dedicated centers [2, 3]. Follow-up studies have shown that most EA patients have a favourable long-term outcome despite persistant digestive and respiratory problems. Common gastrointestinal symptoms after EA repair are dysphagia and gastroesophageal reflux (GER) in up to 72% and 67% of the patients, respectively [4, 5]. Chronic GER after EA repair might lead to mucosal damage, esophageal stricturing, Barrett's esophagus and eventually esophageal adenocarcinoma (EAC) [5-8]. Data on incidence and risk factors for esophageal carcinogenesis after EA repair are scarce [8-10]. The recent ESPGHAN-NASPGHAN guideline recommends routine endoscopy in adults born with EA [11]. Until now, eight cases of esophageal cancer in young EA patients have been described: five esophageal squamous cell carcinoma (ESCC) and three EAC [10, 12-15]. Here we report four EA patients who developed a carcinoma of the gastrointestinal tract: three esophageal carcinoma and one colorectal carcinoma in a colonic interposition. These cases emphasize the importance of lifelong screening and surveillance of the upper gastrointestinal tract in EA patients.

Case 1

Patient A presented for the first time with esophageal carcinoma at age 45 years. He was born with EA Gross type C (with a distal TEF) which was surgically repaired with closure of the fistula and end-to-end anastomosis of the esophagus. In childhood he had undergone a number of esophageal dilations to treat an anastomotic stricture.

At the age of 37 years he developed progressive dysphagia. Upper endoscopy showed proximal esophagitis and a stenotic anastomosis, which then was dilated. No biopsies were taken. Eight years later, dysphagia for solid foods reoccurred with complaints of heartburn and weight loss of 6 kg in six months (BMI 21.6 kg/m2). He was a tobacco smoker (at least 27 pack years) and used 3-4 alcoholic beverages per day. Upper endoscopy showed a non-stenotic anastomosis at 30 cm from the incisors with a ¾ circular growing easily bleeding lesion from 33-42 cm from the incisors. Biopsies showed chronic inflammation. A chest CT scan revealed a stenotic esophagus extending from the aortic arch to the cardia with a malignant appearance and mediastinal lymph nodes (pre- and subcarinal). Due to the strong suspicion of esophageal cancer an esophageal resection with gastric tube reconstruction was performed. Pathology results confirmed the diagnosis of a squamous cell carcinoma (SCC) of the distal esophagus (pT2N0M0) which did not need further treatment.

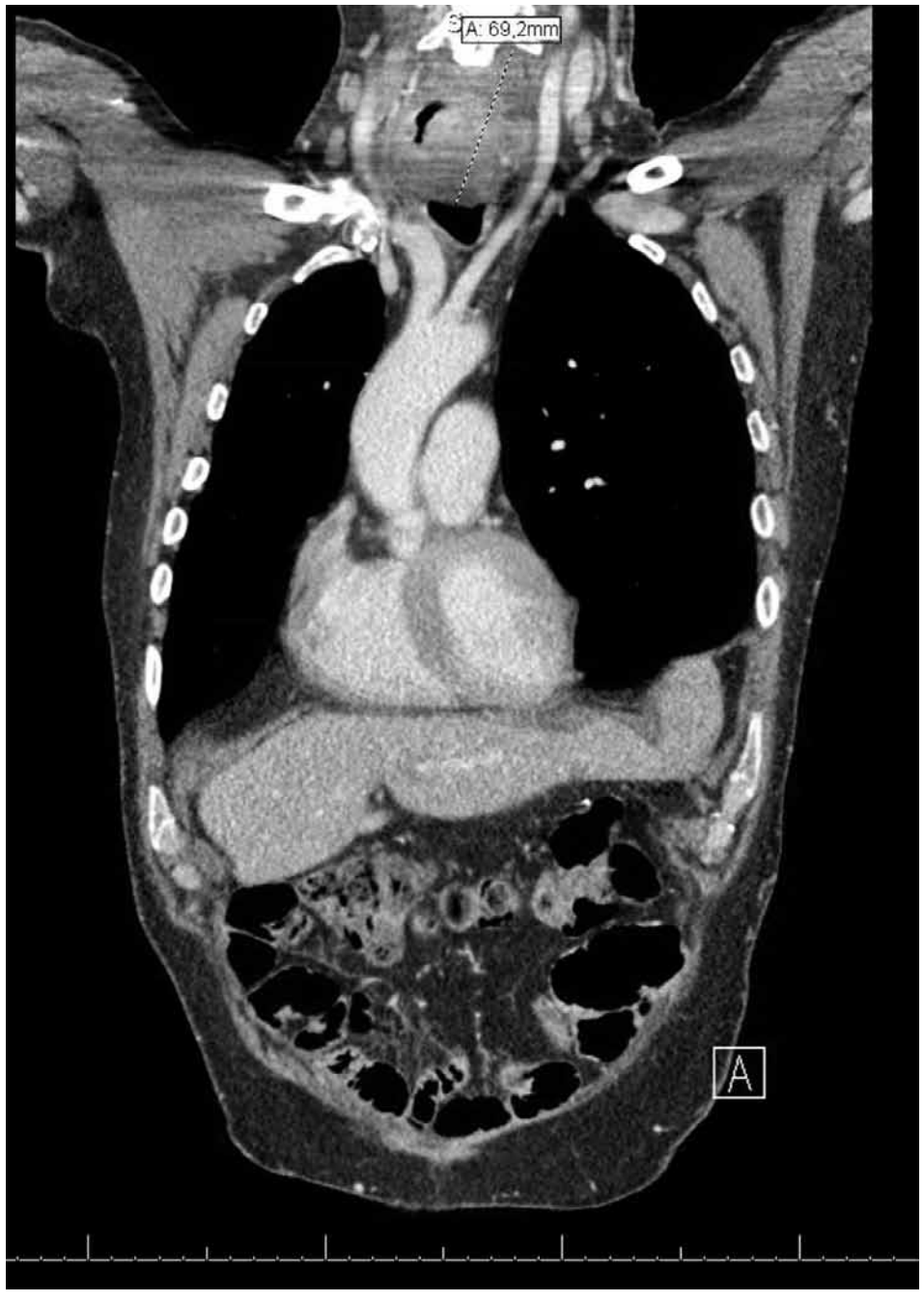


Figure 7.1 Chest computed tomography scan (CT scan) (case 1, tumor 2) demonstrating a tumor mass in the cervical native esophagus with suspected tumor invasion in the left thyroid gland.

Fifteen years later, at the age of 60 years, he again developed dysphagia and odynophagia with 7 kg weight loss (BMI 23.2 kg/m^2). Endoscopy revealed a circular tumor (17-21 cm from incisors) in the remaining cervical native esophagus eroding the constructed gastric tube and trachea. Biopsies showed a well-differentiated SCC. One suspicious supraclavicular and two mediastinal FDG-positive lymph nodes were seen on PET-CT scan images and tumor invasion in the left thyroid gland was suspected FIGURE 7.1. Given the long interval between the two malignancies, this new tumor (T4bN2M0) was most likely a second primary tumor in the remaining cervical esophagus. In a multidisciplinary team discussion it was decided to treat with induction chemotherapy (carboplatin/paclitaxel). Initially the tumor responded well, but four months later he suffered from progressive disease with fistula formation to the trachea which was a contraindication for additional radiotherapy. An esophageal stent was placed to manage progressive dysphagia and palliative radiotherapy (13 x 3 Gy) was started to manage neuropathic pain caused by tumor invasion with imminent spinal cord compression. He died two days later.

Case 2

Patient B was a 42-year old man born with VACTERL association (acronym: vertebral anomalies, anal atresia, cardiac anomalies, TEF, renal anomalies, and limb defects) [16] including EA Gross type A (long gap without TEF), anorectal malformation, coccyx agenesis and vertebral anomalies. Continuity of the esophagus was restored with a delayed end-to-end anastomosis.

At 37 years of age he presented with dysphagia. Upper endoscopy revealed a stenotic anastomosis at 30 cm from the incisors, which could be easily dilated. In the next two years he underwent another three esophageal dilation procedures because of recurrent dysphagia. Biopsies revealed chronic and active inflammation with presence of hyphae. At the age of 42 years he presented with progressive dysphagia, without weight loss (BMI 17.6 kg/m^2). He smoked tobacco and drank alcoholic beverages only in the weekend. This time upper endoscopy revealed a circular stenotic ulcerative ESCC in the proximal esophagus (22-29 cm, anastomosis not visible) FIGURE 7.2A. Endoscopic ultrasound findings were suspicious for tumor invasion in the trachea and several potentially malignant regional lymph nodes (T4N2M0). The tumor was considered unresectable due to invasion of surrounding vital structures (cT4b) FIGURE 7.2B, lymph node metastases, previous thoracotomies (both sides) and intra-mediastinal surgery. Induction chemotherapy (paclitaxel/carboplatin) was started to which the tumor evidently had responded after 2 mo. Concomitant chemoradiotherapy was given (28 x 1.8 Gy) with curative intent. Six years after treatment he shows no signs of recurrent or metastatic disease.

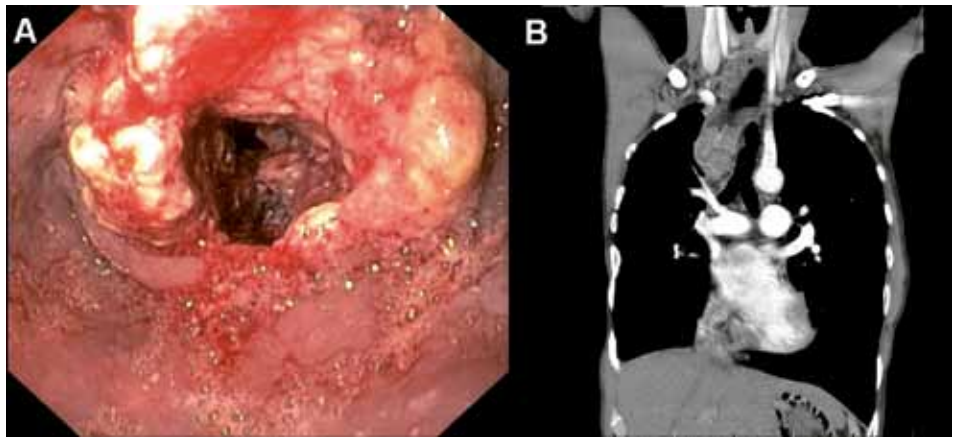


Figure 7.2
Findings at upper endoscopy and chest computed tomography scan (CT scan) (case 2).
A: Upper endoscopy revealing a stenotic ulcerative tumor in the proximal esophagus, 22-29 cm from incisors. Histological examination of esophageal biopsies confirmed the diagnosis esophageal squamous cell carcinoma.
B: Chest CT scan showing a tumor mass in the proximal esophagus with suspected tumor invasion in the trachea.

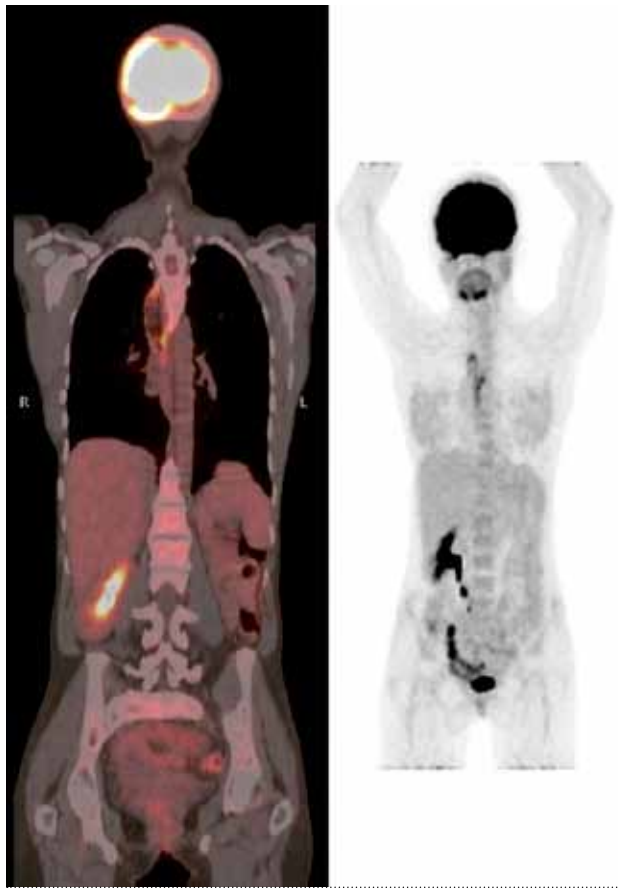


Figure 7.3
Initial findings at positron emission tomography-computed tomography scan (PET-CT scan) (case 3), showing PET-positive lesion in the distal esophagus without metastasis.

Case 3

Patient C presented at the age of 36 years. She was born with an EA Gross type A which was surgically repaired with an end-to-end anastomosis using Livaditis elongation procedure at one month of age. At one year of age she underwent a Nissen fundoplication for severe GER. At the age of 3 years, an anastomotic stricture developed which was treated with repeated esophageal dilations. At the age of 22 years she presented with chronic respiratory symptoms, severe pneumonia, persistent GER, and dysphagia complaints. Upper endoscopy with esophageal biopsies showed no abnormality. In view of the respiratory and gastrointestinal symptoms a duodenal diversion procedure (partial antrectomy with Roux-en-Y gastrojejunal anastomosis) was performed at the age of 23 years.

At 36 years of age she presented with food impaction and weight loss of 4 kg (BMI 14.9 kg/m^2). She did not smoke tobacco and did not drink alcoholic beverages. Upper endoscopy revealed a stenotic ulcerative tumor in the distal esophagus with proximal dilation of the esophagus (25-32 cm from the incisors, gastroesophageal junction at 34 cm, anastomosis not visible). Biopsies revealed a well differentiated SCC. PET-CT scan FIGURE 7.3 and bronchoscopy did not reveal any metastasis. She underwent a subtotal esophagectomy with total gastrectomy and a colonic interposition (pT1bN0M0). Within the following month she required reoperation for a cervical fistula and mediastinitis and underwent two endoscopic dilations of an anastomotic stricture without any evidence of tumor recurrence. Twelve months after surgery she was diagnosed with pleural and bone metastases for which she recently has started palliative chemotherapy.

Case 4

Patient D presented at the age of 47 years. He was born with VACTERL association [16] (EA Gross type C, anorectal malformation, congenital urethral valves with bilateral vesicoureteral reflux and hydronephrosis left kidney). At day 5 after birth a thoracotomy was performed with TEF closure, gastrostomy and cervical esophagostomy placement. In addition the anorectal malformation was corrected. Nine days later a recurrent TEF was ligated. At day 29 the distal esophagus was ligated directly above the stomach and after 7 mo a colonic interposition was constructed. The spleen was congested and therefore resected during this surgery. Revision was needed because of leakage of the proximal anastomosis 19 days later. At 2.5 year of age the gastrostomy was closed. Other medical history included asthmatic bronchitis, bilateral orchidopexy, transurethral resection of urethral valves and nephrectomy of an afunctional infected left kidney.

The research described in this thesis concerns gastrointestinal morbidity after esophageal atresia (EA) repair in both childhood and adulthood. This thesis aims to optimize long-term gastrointestinal follow-up of EA patients.

As survival rates after EA repair are approaching 100%, the focus of medical care for these patients has shifted from mortality to long-term morbidity. Gastrointestinal, respiratory and neurodevelopmental problems as well as growth impairment are common after EA repair [1-3]. Some of these morbidities do not only exist in childhood, but persist during adolescence and through adulthood and may affect quality of life and survival of EA patients. Multidisciplinary follow-up seems necessary after EA repair, however it was not until recently that recommendations on gastrointestinal and nutritional management were missing. In the recently published ESPGHAN-NASPGHAN guidelines several aspects of gastrointestinal and nutritional complications are highlighted [4]. Various of these complications are discussed in this thesis i.e. growth impairment (Chapter 2), gastroesophageal reflux (GER; Chapter 4), esophageal strictures (Chapter 5), Barrett's esophagus (BE; Chapter 6) and esophageal cancer (Chapters 6 and 7) FIGURE 8.1.

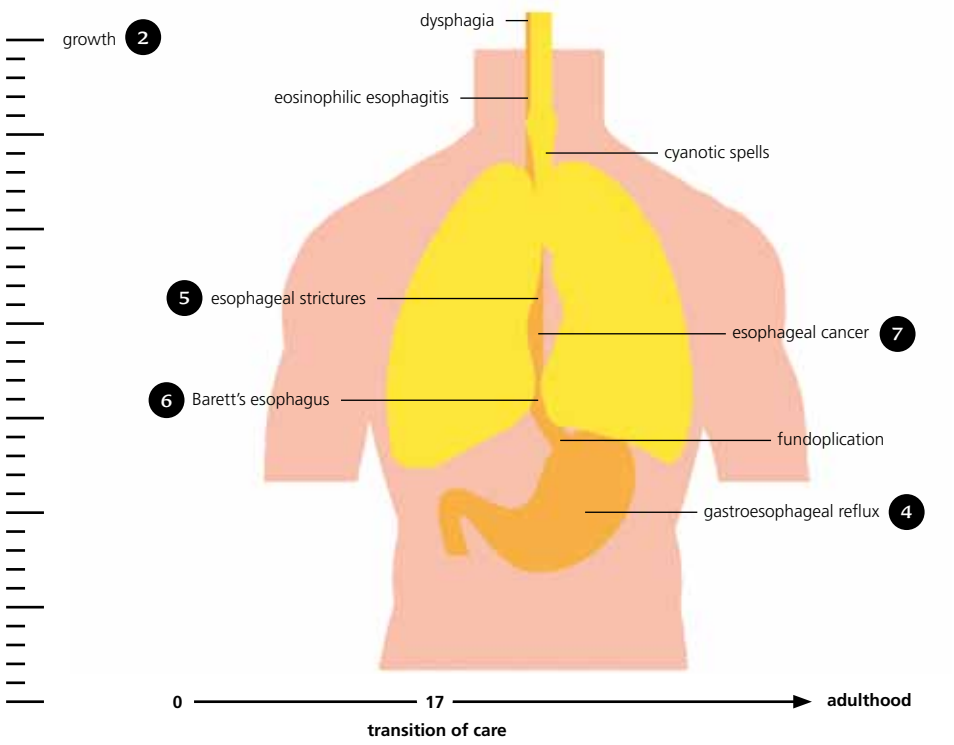


Figure 8.1 Gastrointestinal and nutritional complications in esophageal atresia patients.

In 1999, a longitudinal follow-up program was started at the Pediatric Surgery department of our center [5, 6]. All children born with a major anatomical malformation (e.g. EA, congenital diaphragmatic hernia and omphalocele) have joined this program since. A multidisciplinary team runs this program, with scheduled visits until 18 years of age and transfer for adult care when the child turns 17 years. The program aims to reduce overall morbidity associated with these anatomical malformations and has resulted in valuable long-term follow-up data for these specific patient groups. Chapters 2 and 4 evaluated data obtained from EA patients participating in this longitudinal follow-up program.

Feeding difficulties and growth impairment

The first years of life are crucial for normal development of the brain and immune system [7, 8]. With a brand new connection between the native esophagus and stomach, neonates treated for EA are confronted with the first gastrointestinal challenges in life. Accompanied by dysphagia, regurgitation, burping, vomiting, coughing, and choking it is a challenge for these neonates to achieve required nutritional intake. Feeding difficulties after EA repair are the result of oropharyngeal dysfunction, esophageal dysfunction and/or behavioral disorders, and reduce with age [9-11].

A study in 56 children born with EA (median age 3.7 years; range 0-16.8 years) showed that 54% of children were not eating age appropriate textures (72% of children aged 0-2 years) [10]. Another study comparing 124 children treated for EA with 50 control patients, found late introduction of solid foods, prolonged meal times, more episodes of chocking/coughing during meals, and more refusal of meals in EA patients [12]. In 40 children treated with delayed primary repair for long-gap EA, normal development of feeding skills were found despite the late onset of feeding in these patients [13]. Although feeding difficulties are common after EA repair [11], children with the most common type of EA (Gross type C) seem to have mild (subclinical) feeding difficulties, while severe problems are observed in patients with Gross type A EA and extreme prematures [14]. Early dietary management to achieve a good nutritional status seems warranted in these patients.

Low birthweight is a risk factor to develop underweight and a short stature [15]. As many EA patients are born small for gestational age (30%) or prematurely (36%-39%), these children – compromised by feeding problems and recurrent infections – are at risk of growth impairment [16-19].

To date, studies on growth in children born with EA are mainly cross-sectional or retrospective [10-12, 20-28]. Several studies found a reduced height in children with EA [10-12, 20, 22-24, 27, 28]. In the Rotterdam EA cohort, we published two longitudinal studies found impaired growth (height)

119 Hashimoto, C.L., et al., *Lugol's dye spray chromoendoscopy establishes early diagnosis of esophageal cancer in patients with primary head and neck cancer*. Am J Gastroenterol, 2005. **100**(2): p. 275-82.
120 *European Reference Network on rare intestinal, Inherited and Congenital Anomalies (ERNICA)*. Available from: https://ern-ernica.eu/.

9

Summary
Nederlandse samenvatting

APPENDICES

LIST OF ABBREVIATIONS

	Abbreviations
BE	Barrett's esophagus
BCT	bolus clearance time
BMI	body mass index
CI	confidence interval
CT scan	computed tomography scan
DTH	distance-to-height
EA	esophageal atresia
EAC	esophageal adenocarcinoma
ESCC	esophageal squamous cell carcinoma
GEJ	gastroesophageal junction / gastric folds
GER	gastroesophageal reflux
GERD	gastroesophageal reflux disease
GM	gastric metaplasia
GOR	gastro-oesophageal reflux
GORD	gastro-oesophageal reflux disease
HFA	height-for-age
IM	intestinal metaplasia
IQR	inter-quartile range
ISFET	ion-sensitive field-effect transistor
MMS	Medical Measurement Systems
OA	oesophageal atresia
PET-CT scan	positron emission tomography-computed tomography scan
pH-MII monitoring	pH and impedance monitoring
PPI	proton pump inhibitor
RBM	retrograde bolus movements
RI	reflux index
SAP	symptom association probability
SD	standard deviation
SI	symptom index for reflux
SDS	standard deviation score
SGA	small for gestational age
TEF	tracheoesophageal fistula
TH	target height
TOF	tracheo-oesophageal fistula
VIFs	variance inflation factors
WFH	weight-for-height