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

Floor W.T. Vergouwe

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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

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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].

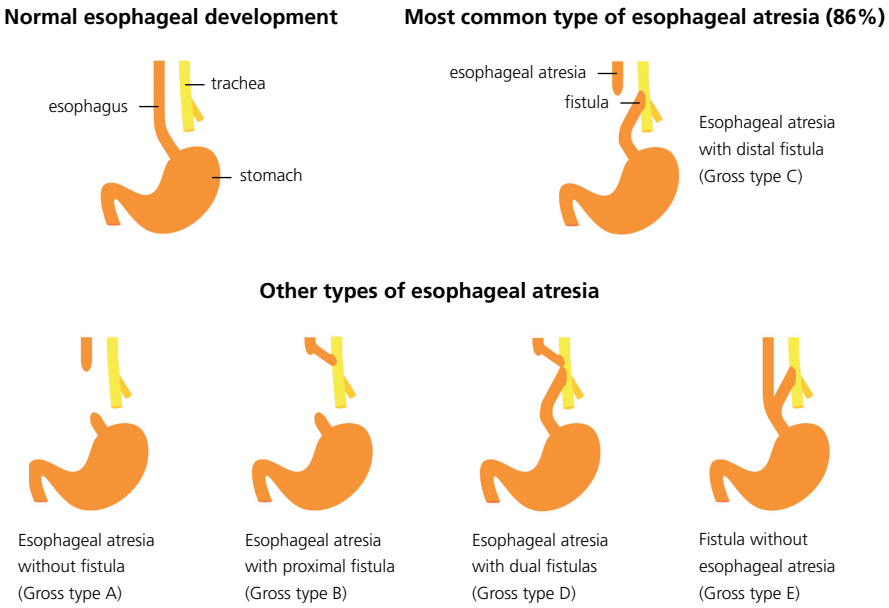

Figure 1.1 Normal esophageal development and the five types of esophageal atresia (Gross types A, B, C, D and E).

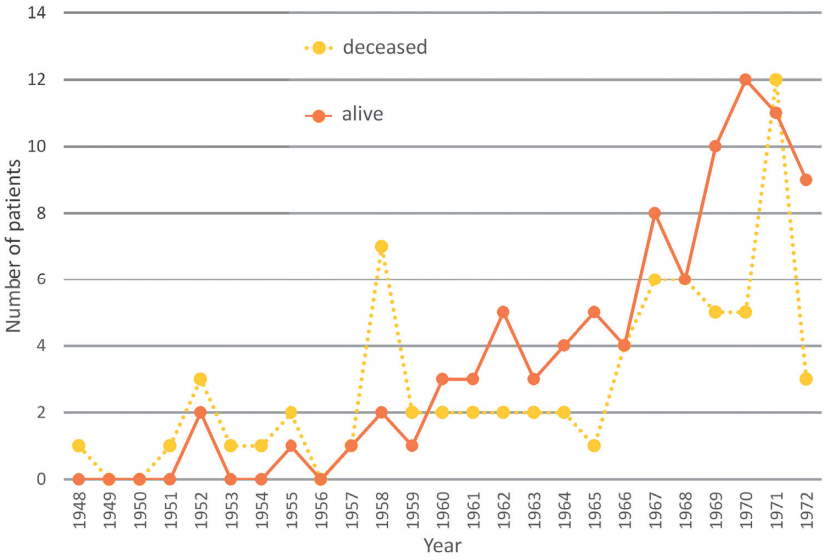

Figure 1.2 Children born with EA and treated between 1948 and 1972 in the Erasmus MC-Sophia Children's Hospital in Rotterdam (Figure adapted from EUR thesis van Walleghem 1973).

In The Netherlands surgical repair of EA and TEF takes place in all university hospitals involved in neonatal surgery. Each year around 10-15 newborns with EA and/or TEF are admitted to the Intensive Care Unit of the Erasmus MC-Sophia Children's Hospital in Rotterdam. Since 1999, all children born with EA have joined a longitudinal follow-up program at the Pediatric Surgery department, with scheduled visits until 18 years of age and transfer for adult care [16, 17].

Researchers of our center previously published data on growth up to 5 years of age, long-term respiratory problems, long-term neurodevelopmental problems and genetics in EA patients [18-25]. This thesis focuses on gastrointestinal morbidity after EA repair.

Gastroesophageal reflux and associated gastrointestinal problems

After EA repair, esophageal dysmotility is present in almost all patients [26]. Several patho-physiological mechanisms underlying disturbed esophageal motility in EA patients have been suggested. Inborn deficient esophageal innervation and abnormal esophageal smooth muscle development seem to play a role, but also surgical injury to the vagal nerve and esophageal damage caused by surgical complications (e.g. anastomotic leakage, anastomotic strictures and subsequent dilation procedures) are thought to be related to dysmotility in EA patients [27-33].

Esophageal motility disorders might lead to aspiration, gastroesophageal reflux (GER), complaints of dysphagia and feeding problems with associated growth impairment.
A systematic review of chronic long-term problems in EA patients found a high prevalence of GER symptoms of 40.2% compared to 10%-20% in the general population [34, 35]. However, no uniform definition to define GER was used which complicates comparing results from different studies. The gold-standard test for the diagnosis of GER is pH monitoring with or without impedance monitoring [36]. Both pH and impedance monitoring measure the acid reflux burden. The additional value of impedance monitoring is the ability to detect non-acid reflux and is therefore a good diagnostic tool to evaluate the correlation between symptoms and (acid and non-acid) reflux events [36-38].

Since it is unlikely that there is an absolute cut-off value that distinguishes pathologic from physiologic GER, the NASPGHAN-ESPGHAN guideline on GER suggests to consider a reflux index between 3% and 7% to be indeterminate (abnormal and normal index: >7% and <3%, respectively) [36]. A Danish study found an abnormal reflux index in 32/58 (55%) children with EA aged 5-15 years [39].

As gastrointestinal problems – including GER – are prevalent in EA patients, recent NASPGHAN-ESPGHAN guidelines for the management of gastrointestinal complications in children with EA were developed [38]. GER is already present in the neonate and often continues into early childhood and adulthood. Long-term exposure of the esophagus to GER might lead to esophageal damage including esophagitis, esophageal strictures, Barrett's esophagus (BE) and eventually esophageal adenocarcinoma [40-43]. To diminish associated complications early diagnosis and treatment of GER is important.

The recommendations in the recent guidelines for the management of gastrointestinal complications in children with EA (published in 2016) are mainly based on expert opinions, as only a few randomized controlled trials in EA patients were available [38]. The guidelines recommend to treat all EA patients with acid suppression in the neonatal period up to the age of one year [38]. At time of discontinuation of acid suppression, it is recommended to monitor GER using combined impedance and pH monitoring to evaluate the need for continuation of acid suppression [38]. Since GER can be asymptomatic, it is advised to perform three routine endoscopies in asymptomatic children: one after discontinuation of acid suppression, one before the age of 10 years and one at transition to adulthood [38].

Anastomotic stricture formation is the most frequent complication after EA repair, present in up to 59% of EA patients [44]. The newest ESGE-ESPHGAN guideline on pediatric endoscopy defines a refractory stricture of the esophagus as 'an anatomic stricture without endoscopic inflammation that results in dysphagia after a minimum of five dilations at maximally four-week intervals' [45]. Frequent dilation procedures in these children result in a high burden for both child and parents.

As GER is present since early childhood, concerns in adult EA patients include development of BE and esophageal carcinoma. Eight esophageal carcinoma have been reported in young adult EA patients [46-52], but it was not until recently that esophageal surveillance has been suggested in this group of patients. The recent guidelines recommend surveillance endoscopy every five to ten years to detect early signs of esophageal metaplasia or malignancy, but the ideal endoscopic surveillance strategy has yet to be determined [38].

Due to the absence of clinical practice guidelines on care for EA patients beyond childhood, hospitals have lost sight of adult EA patients over the years [53]. This is enhanced by the fact that EA patients do not easily seek medical help for gastrointestinal complaints, as they may have gotten used to these symptoms over the years. As a result, the burden of long-term gastrointestinal problems in adult EA patients is still unclear.

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).

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2

Longitudinal evaluation of growth in esophageal atresia patients up to 12 years

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ABSTRACT

Background and aims

Previous studies reported diminished growth after oesophageal atresia (OA) repair. We evaluated long-term follow-up data on growth.

Methods

Longitudinal cohort study up to 12 years. Patients with OA, born 1999-2013, who participated in a longitudinal follow-up programme were included. Children with genetic syndromes associated with growth disorders were excluded. SD scores (SDS) for height-for-age (HFA), weight-for-height (WFH) and distance-to-target-height were calculated for routine visits (0.5/1/2/5/8/12 years). Linear mixed models were used to estimate SDS until 12 years of age and to evaluate explanatory factors for growth.

Results

We included 126/155 children (32% prematurely born, 20% small for gestational age), 32 reached the age of 12 years. Fundoplication surgery was performed in 24%. SDS-HFA was below normal up to 8 years but improved over these years (mean (SE) -0.48 (0.09), -0.31 (0.09) and -0.20 (0.13) at 0.5, 8 and 12 years). Scores improved after correction for target height (mean (SE) -0.29 (0.10), -0.17 (0.09) and -0.10 (0.14) at 0.5, 8 and 12 years). SDS-WFH was below normal from age 1-5 years (mean (SE) -0.53 (0.09), -0.24 (0.09) and 0.03 (0.14) at 1, 5 and 12 years). Low birth weight and fundoplication surgery were negatively associated with growth.

Conclusions

The growth of patients with OA was below the reference norm during the first years of life, but normalised at 12 years. Large longitudinal cohort studies should evaluate if normal growth persists into adolescence. Early nutritional assessment with timely dietary intervention should be considered especially in those with low birth weight or following fundoplication surgery.

INTRODUCTION

Oesophageal atresia (OA) is a rare anatomical anomaly which occurs in 2.43 per 10,000 births worldwide [1]. Over the past decades, survival rates have improved to up to 95% [2, 3]. While OA outcome research used to focus on respiratory or gastrointestinal morbidity, we have come to realise that growth is an important outcome measure too. Many of these children are born small for gestational age (SGA) or prematurely [1, 4], and growth might be compromised by feeding difficulties, gastrointestinal problems, recurrent pulmonary infections, associated congenital malformations and genetic syndromes.

Most studies on growth in patients with OA are cross-sectional or retrospective [5-16]. Our group previously published longitudinal data on growth, which suggested persisting growth impairment up to 5 years [17].

We therefore hypothesised that children with OA face growth problems at the longer term, notably if serious comorbidity is present. We longitudinally evaluated the growth of patients with OA from infancy up to school age. Moreover, we searched for determinants of growth impairment.

MATERIALS AND METHODS

Population

We included patients with OA born between 1999 and 2013, who after birth were admitted to the Intensive Care Unit of the Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands, and since then participate in a longitudinal follow-up programme. Physical health, growth, lung function when appropriate and developmental parameters are regularly assessed until 17 years of age [17]. Parents were informed about the study. The Medical Ethics Committee of Erasmus MC concluded that the Medical Research Involving Human Subjects Act did not apply to the study protocol (protocol ID MEC-2016-111). Data were included until December 2015. Data from children with genetic syndromes known to be associated with growth disorders were excluded.

Study design

The following general data were retrieved: gender, ethnicity, gestational age, birth weight, type of OA according to Gross [18], associated anomalies, type of primary oesophageal surgery, initial days on ventilator and parental height. In addition, specific data were retrieved related to growth status (baseline and at follow-up): height, weight, type of feeding, diagnosis of

gastrooesophageal reflux (GOR), therapy for GOR, pulmonary infections, use of antibiotics (prophylaxis or therapeutic dose), number and duration of hospital admissions, number of surgical interventions and number of dilations of oesophageal stenosis.

Comorbidity was classified as major or minor. Major comorbidities included Ravitch' paediatric surgical index diagnoses [19], cardiac malformations requiring surgical correction or follow-up by a paediatric cardiologist, other congenital malformations requiring major surgical interventions, and malformations seriously affecting normal function (eg, tethered cord with neurogenic bladder function). All other anomalies were considered minor (eg, small atrial septal defect closing spontaneously). VACTERL association was defined according to Solomon et al. [20] Prematurity was defined as a gestational age <37 weeks. SGA was defined as a birth weight 2 SDs below normal [21]. High-calorie nutrition included fortified breastmilk, additives such as soybean fat, and concentrated formula. GOR was considered clinically significant if fundoplication surgery was performed, if pH monitoring showed pathological reflux or if upper endoscopy showed typical reflux-induced mucosal lesions [22]. Besides, spontaneous GOR extending to the proximal oesophagus at contrast oesophagography with typical symptoms was diagnosed as GOR. GOR was classified as either adequately treated (fundoplication surgery performed, medical therapy without symptoms or normal pH monitoring during treatment) or insufficiently treated (ie, clinical symptoms, symptomatic spontaneous GOR in proximal oesophagus or presence of GOR during pH monitoring despite medical therapy). Pulmonary infections were defined as lower respiratory tract infections requiring antibiotics and/or hospital admission.

Physical growth

Physical growth was evaluated by weight and height measurements at 0.5, 1, 2, 5, 8 and 12 years of age. SD scores (SDS) were calculated for height-for-age (HFA) using the populationspecific reference data from the Fifth Dutch Growth Study (2009) [23]. SDS for weight-for-height (WFH) were calculated using normative references [24]. SDS-HFA was corrected for Moroccan or Turkish ethnicity if applicable [25]. We corrected for prematurity until 2 years of corrected age. Target height (TH) and its SDS were calculated with parental heights as previously described [26]. SDS for distance-to-target-height (SDS-DTH) was calculated as SDS-HFA minus SDS-TH. Wasting (acute malnutrition) and stunting (chronic malnutrition) were defined as, respectively, WFH and HFA >2 SD below normal [27].

Data analysis

Data are summarised as percentages, mean (SD or SE) or median (range), as appropriate. To evaluate growth longitudinally, we used linear mixed models for the repeated measurements of growth SDS [28]. In the linear mixed models, the dependent variable consisted of SDS for

HFA, DTH and WFH at 0.5, 1, 2, 5, 8 and 12 years of age. The following variables were considered for inclusion as explanatory variables: assessment age (coded as a categorical variable), birth weight, OA Gross type A, VACTERL association or major anomalies, thoracotomy, duration of initial ventilation, fundoplication surgery (coded as a time-dependent dichotomous variable: negative before and positive after fundoplication), number of surgeries, history of GOR, occurrence of pulmonary infections in the previous year and number of dilation procedures. Three models (for SDS-HFA, SDS-DTH and SDS-WFH) were fitted using a stepwise backward approach (p-value cut-off of 0.20). An unstructured covariance matrix was used to account for the within-subject correlations. After the stepwise backward variable selection, statistically significant interaction effects of assessment age and each of the other selected explanatory variables were included. Multicollinearity was assessed using variance inflation factors (VIFs). All VIFs were <2.5, suggesting that multicollinearity was not a problem [29].

For each growth parameter two other linear mixed models were estimated, one with only assessment age, and one with assessment age, fundoplication and their interaction term included as explanatory variables. The results of these linear mixed models were summarised using the estimated marginal means, which are the mean predicted values of the dependent variable (growth SDS) adjusted for the effect of explanatory variables. These estimated marginal means were used to compare the mean SDS for growth parameters with the norm in the reference population (SDS=0).

The statistical analyses were performed using SPSS V.21.0 for Windows (IBM, Chicago, Illinois, USA) with a two-sided significance level of 0.05.

RESULTS

Demographic characteristics

Of the 155 children born with OA in the study period, 126 were included (see exclusion details in FIGURE 2.1). Reasons for missing growth data were refusal (n=11), emigration (n=7), follow-up performed at another age for organisational reasons (n=3), follow-up at other hospital (n=1), lost to follow-up (n=1) and no length measurement available (n=1). Variation in age of all children attending visits is available in SUPPLEMENTARY TABLE 2.1. TABLE 2.1 summarises demographics. Male sex predominated; almost one-third were born prematurely and almost one-fifth were born SGA. Vertebral anomalies, anal atresia, cardiac anomalies, tracheo-oesophageal fistula, renal anomalies, and limb defects (VACTERL) association or major anomalies were reported in 32 (25.4%) children. Nearly half of the children (n=59; 46.8%) were extubated on the first postoperative day. Fifty-four children were extubated after 2-7 days, 8 after 8-14 days, 2 after 14 days and 3 after more than a month (37, 41 and 43 days, respectively).

In 12 (9.5%) children primary surgery consisted of a gastrostomy (Gross type A/B/C in 5/1/6, respectively). Anastomosis was obtained in all but one child at a median age of 78 (30-143) days.

Thirty-nine (31.0%) children used high-calorie nutrition. Tube feeding or parenteral nutrition was discontinued in 29 (60.4%) children before the 6-month visit. At 5 years of age, 4 (4.1%) children still used high-calorie nutrition and 2 (2.1%) children still needed (supplemental) tube feeding.

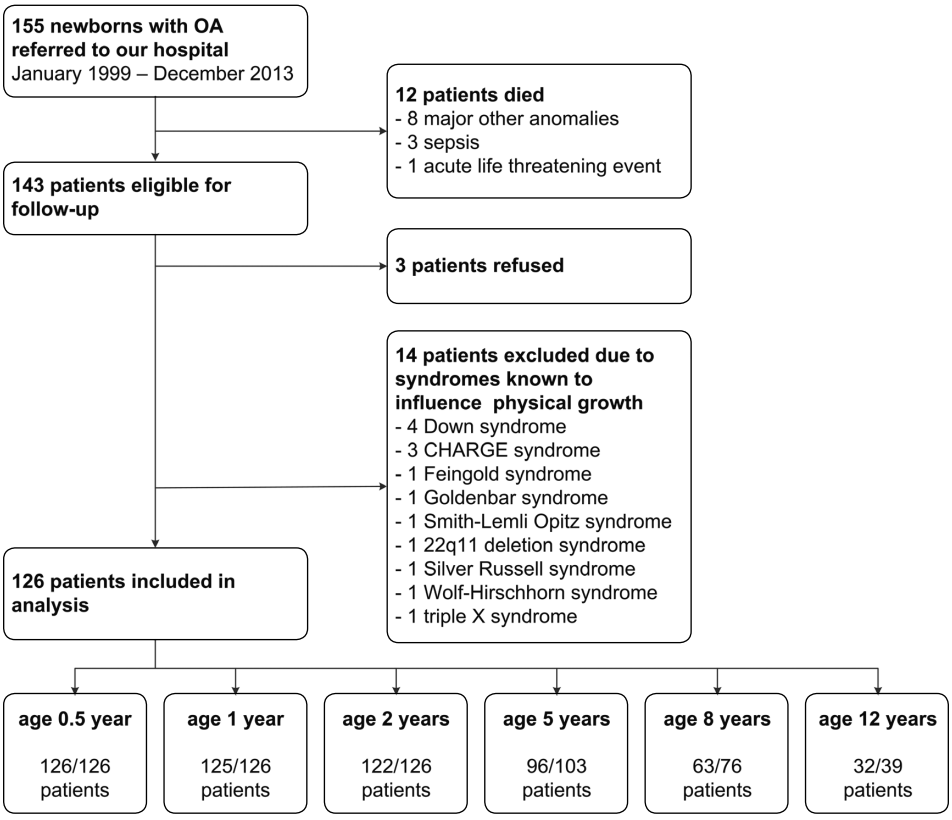

Figure 2.1 Enrolment of patients with oesophageal atresia (OA) (N=126). For each routine visit, the actual number of patients of whom growth data were obtained and the number of patients who reached the specified age of the visit are shown. CHARGE, coloboma, heart defects, atresia of the choanae, retardation of growth, genital and urinary abnormalities, ear abnormalities and/or hearing loss.

Table 2.1 Patient demographics (N=126)

	n (%)
Males	78 (61.9)
Ethnicity	
- Dutch	109 (86.5)
- Moroccan	6 (4.8)
- Turkish	5 (4.0)
- Other	6 (4.8)
Gestational age (weeks); median (range)	38.3 (25.6-42.3)
Prematurity	40 (31.7)
Birthweight (kilogram); median (range)	2.830 (0.725-4.505)
SGA	25 (19.8)
Type of OA	
- Type A	5 (4.0)
- Type B	1 (0.8)
- Type C	114 (90.5)
- Type D	3 (2.4)
- Type E	3 (2.4)
Type of oesophageal correction	
- Primary anastomosis	111 (88.1)
- Delayed anastomosis	11 (8.7)
- Gastrostomy [a]	1 (0.8)
- Ligation of tracheo-oesophageal fistula	3 (2.4)
Type of surgery	
- Thoracoscopy	42 (33.3)
- Thoracotomy	81 (64.3)
- Converted	3 (2.4)
Associated problems	
- Major associated problems	28 (22.2)
- VACTERL association	16 (12.7)
- Minor associated problems	38 (30.2)
Initial days on ventilator; median (range)	2 (0-73)
Initial hospitalization (days); median (range)	23 (7-464)
Hospital admissions in first 2 years of follow-up; median (range)	
- Number of admissions	3 (1-19)
- Duration (days)	41 (8-467)
Feeding type at initial discharge	
- No tube feeding	78 (61.9)
- (supplemental) tube feeding [b]	47 (37.3)
- Parenteral nutrition	1 (0.8)
History of GOR [c]	56 (44.4)
Fundoplication surgery [d]	30 (23.8)
Dilation of oesophageal stenosis [e]	75 (59.5)
History of pulmonary infection(s)	102 (81.0)
Prophylactic antibiotics [f]	54 (42.9)

GOR, gastro-oesophageal reflux; OA, oesophageal atresia; SGA, small for gestational age.

a No oesophageal continuity was obtained in one patient with a long-gap OA.

b Discharge with (supplemental) nasal gastric tube (n=35), nasal jejunal tube (n=1), gastrostomy (n=10) or jejunostomy (n=1) feeding.

c First diagnosis of GOR: fundoplication surgery performed (n=25), pathological pH monitoring (n=28), typical reflux-induced lesions during endoscopy (n=1), pathologic contrast oesophagography with typical symptoms (n=2).

d Nissen (n=29) or Thal fundoplication (n=1) performed at a median age of 175 (range 54–1343) days. Redo-fundoplication was needed in four patients, with a median time interval after initial fundoplication surgery of 253 (range 91–434) days. Two redo-fundoplication surgeries were performed in one patient.

e Median of 2 (range 1–15) dilations.

f Number of patients with prophylactic antibiotic treatment for respiratory and/or urinary tract infections.

At each routine visit until the 8-year visit, half of the children received antibiotic treatment for respiratory tract infections (prophylaxis or therapeutic dose); at the 12-year visit this was the case for only 21.9%. Prophylactic antibiotics for respiratory or urinary tract infections were given to 42.9% of the children, mostly in the first 2 years.

Eighty-three per cent (n=105) of children had been readmitted before the 6-month visit. Readmission rates since their last visit were around 30% for the periods 0.5-1, 1-2 and 2-5 years. Only 16% had been admitted between 5-8 and 8-12 years.

Fundoplication surgery was needed in 30 (23.8%) children. Indications were apparent life-threatening events suspected of GOR (n=15), recurrent oesophageal strictures in combination with oesophagitis (n=5) or feeding difficulties (n=6), vomiting with oesophagitis (n=2) and persistent acidic GOR despite adequately dosed anti-acid drug therapy (n=2). In 24 patients, a reliable pH monitoring was obtained prior to fundoplication, in 70.8% (n=17) GOR was confirmed. Surgeries other than fundoplication procedures (eg, aortopexy, reconstruction of anorectal/cardiac/limb malformations, pyloromyotomy or closure of recurrent tracheo-oesophageal fistula) were performed in 48.4% (n=61).

Physical growth

TABLE 2.2 summarises all biometric results. SDS-HFA was below the population norm in the first 8 years, but improved over these years. Chronic malnutrition (stunting) was reported in 5%-8% of children (depending on age). After correction for TH, results of HFA were more favourable. SDS-DTH <–2 SD was present in 3%-5% of children. Mean SDS-WFH declined in the first 2 years, after which it improved and normalised at 8 years. Mean SDS-WFH was below the population norm at the ages of 1, 2 and 5 years. Wasting was present in 3%-12% of children.

Determinants of growth impairment

Results of the multivariable linear mixed models are listed in TABLE 2.3 . One or more explanatory variables were missing in 0.5% of the visits, and these visits were excluded from the longitudinal analyses. Lower birth weight and fundoplication surgery, after adjustment for other factors, were associated with lower SDS for all three growth parameters. Children who underwent fundoplication surgery had significantly lower SDS-WFH at their subsequent visits, but this association was age-dependent (interaction term; illustrated in FIGURE 2.2) see SUPPLEMENTARY FIGURES 2.1 AND 2.2 illustrating individual trajectories and for each patient the change in SDS compared with the previous time point). The number of surgeries and history of pulmonary infections were positively associated with WFH.

The linear mixed models did not reveal any significant associations between the growth parameters and OA Gross type A, VACTERL association or major anomalies, thoracotomy, duration of initial ventilation, history of GOR or number of dilation procedures.

Table 2.2 Biometric results for all age groups

Age	SDS-HFA		Stunting	SDS-DTH		SDS-DTH <-2	SDS-WFH		Wasting
years	mean (SE)	p-value	n (%)	mean (SE)	p-value	n (%)	mean (SE)	p-value	n (%)
0.5	-0.479 (0.087)	**<0.001**	10 (7.9)	-0.288 (0.100)	**0.005**	6 (4.8)	-0.164 (0.099)	0.100	9 (7.1)
1	-0.446 (0.090)	**<0.001**	9 (7.2)	-0.280 (0.097)	**0.005**	6 (4.8)	-0.534 (0.094)	**<0.001**	11 (8.8)
2	-0.343 (0.089)	**<0.001**	8 (6.6)	-0.172 (0.095)	0.074	4 (3.3)	-0.624 (0.094)	**<0.001**	15 (12.3)
5	-0.412 (0.092)	**<0.001**	5 (5.2)	-0.271 (0.098)	**0.007**	4 (4.2)	-0.236 (0.093)	**0.013**	3 (3.1)
8	-0.310 (0.090)	**<0.001**	3 (4.8)	-0.173 (0.093)	0.066	2 (3.2)	-0.179 (0.109)	0.104	2 (3.2)
12	-0.197 (0.133)	0.146	2 (6.3)	-0.102 (0.139)	0.468	1 (3.1)	0.028 (0.144)	0.849	1 (3.1)

SDS-HFA, SDS-DTH and SDS-WFH = SD scores for height-for-age, distance-to-target-height and weight-for-height. For each growth parameter, a separate linear mixed model including only assessment age as explanatory variable was estimated. The estimated marginal means were used to compare the mean SDS with the norm in the general population (SDS=0). Bold typeface indicates significance level of 0.05.

Table 2.3 Estimated coefficients of the mixed models for SDS for HFA, DTH and WFH

Mixed model		Estimated coefficient (95% CI)	p-value
SDS-HFA	Assessment age	[a]	**0.001**
	Birthweight; kilogram	0.3791 (0.1807 – 0.5775)	**<0.001**
	Fundoplication surgery performed	-0.3615 (-0.6147 – -0.1082)	**0.005**
	Initial days on ventilator	-0.0147 (-0.0303 – -0.0009)	0.064
SDS-DTH	Assessment age	[a]	**0.001**
	Fundoplication surgery performed	-0.4621 (-0.7364 – -0.1879)	**0.001**
	Birthweight; kilogram	0.3218 (0.1182 – 0.5254)	**0.002**
	Initial days on ventilator	-0.0159 (-0.0331 – 0.0012)	0.069
SDS-WFH	Assessment age	[a]	**0.001**
	Interaction fundoplication surgery with age	[a,b]	**<0.001**
	Number of surgeries performed	0.1277 (0.0411 – 0.2143)	**0.004**
	Birthweight; kilogram	0.2457 (0.0479 – 0.4435)	**0.015**
	History of pulmonary infection(s) [c]	0.1517 (0.0254 – 0.2779)	**0.019**
	Thoracotomy performed [d]	-0.2787 (-0.5911 – 0.0338)	0.080
	VACTERL association or major anomalies	-0.3033 (-0.6552 – 0.0487)	0.091

SDS-HFA, SDS-DTH and SDS-WFH = SD scores for height-for-age, distance-to-target-height and weight-for-height.
Bold typeface indicates significance level of 0.05.

a Estimated coefficients with 95% CIs are not shown for this categorical variable.

b The interaction term represents the age-dependent effect of fundoplication surgery on SDS-WFH after adjustment for the main effect of age and other explanatory variables, but without adjustment for the main effect of fundoplication surgery. The interaction term would also contribute significantly to the model after adjustment for the main effects of both age and fundoplication surgery.

c Occurrence of lower respiratory tract infection(s) requiring antibiotics and/or hospital admission in previous year.

d Thoracotomy performed during primary oesophageal atresia repair.

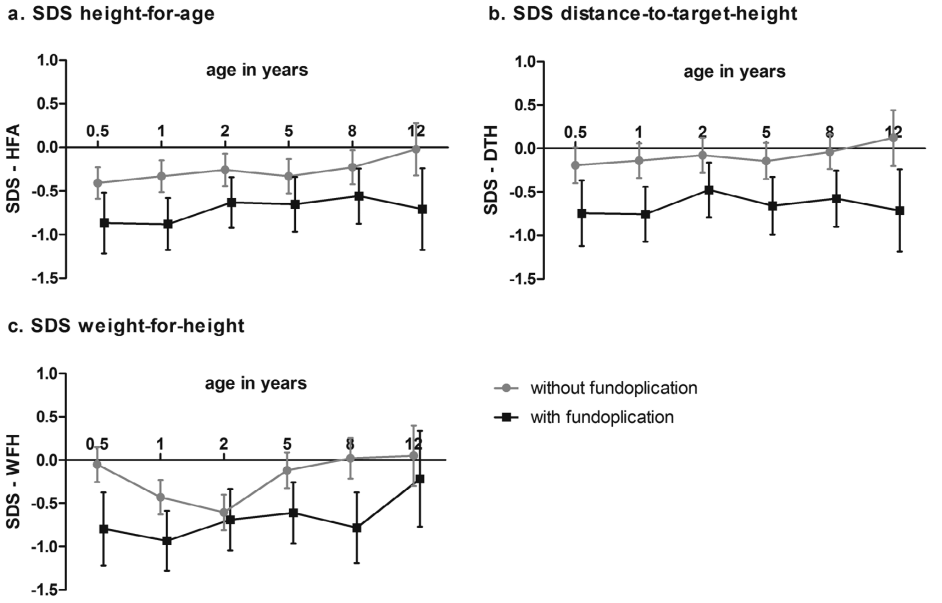

Figure 2.2 Biometric results for SDS-HFA (A), SDS-DTH (B) and SDS-WFH (C) of children with and without fundoplication surgery. Symbols represent the estimated marginal means of the SD scores (SDS) with associated 95% CIs (error bars) for the different growth parameters at the different time points, based on a linear mixed model that includes age, fundoplication and their interaction term as explanatory variables.

DISCUSSION

In this study in 126 children born with OA, we found a significantly lower weight and height in the first 5 and 8 years of life compared with the general population. Weight and height had normalised, however, at 12 years of age. To our knowledge, our study is the first to address DTH in patients with OA. TH can be useful to discriminate the influence of disease on growth [30]. When height was corrected for individual TH, the SDS for height (SDS-DTH) improved. This finding shows the importance of structurally recording parental height, as a child's nutritional status can be underestimated when only interpreting SDS-HFA. Stunting was present in a minority of children and was seen less frequently when children got older. Two of the studied explanatory variables were negatively associated with growth, that is, low birth weight and fundoplication surgery.

Previous studies reported reduced HFA in patients with OA [5, 7-9, 11, 12, 14-16]. Longitudinal data showed growth problems up to 5 years of age with catch-up between 2 and 5 years [17, 31]. HFA was significantly lower in the first 2 years of patients who underwent thoracoscopic repair [31]. The small sample size in the latter study (n=37) limits the strength of the evidence, however.

In our cohort, WFH was found to decline in the first 2 years, indicating acute weight loss. After this age, WFH recovered and had normalised at 8 years of age. Several retrospective and cross-sectional cohort studies described weight below the reference norm in patients with OA [5, 7-9, 11, 12, 15, 16]. Longitudinal data published by our group showed a weight-for-age below the norm during the first 5 years [17]. WFH was significantly lower in a small series of patients with thoracotomic repair [31]. These results warrant early dietary management, as a good nutritional status in the first years of life is crucial for normal brain and immune system development [32, 33].

In this study, patients with OA showed catch-up growth before puberty. We suspect that fewer pulmonary infections and shorter duration of hospitalisation after the first 2 years of life contributed to an early growth spurt [17, 34].

We found two of the studied explanatory variables to be negatively associated with growth. For one, children with a low birth weight were more likely to have a short stature and to be underweight, which is in concordance with previous studies [35]. Second, many children who underwent fundoplication surgery, typically performed in the first 6 months, had height and weight below the reference norm after this surgery (at 12 years only mean SDS-WFH was improved to normal). We suspect that these children have persistent feeding problems preventing catch-up growth. Moreover, they may have had more extreme disease severity posing a risk for failure to thrive. The SDS-WFH of these children increased from 1 to 2 years, which we assume can be ascribed to adequate treatment of severe GOR.

Our finding that number of surgeries and history of pulmonary infections were positively associated with WFH was unexpected. We speculate that children with recurrent hospitalisations more often received dietary interventions. Close involvement of multidisciplinary nutrition support teams was indeed found to prevent failure to thrive in patients with congenital diaphragmatic hernia [36]. It is worth recommending to have such teams, including dietitians and speech-language pathologists, available to support hospitalised children in general, and continue supporting high-risk patients after discharge to home.

Previous studies reported long-gap OA, oesophageal substitution and a history of GOR as explanatory variables for growth impairment [6, 7, 12]. We also evaluated these factors, but did not find associations with growth impairment, perhaps because the sample size is relatively small for multivariable analyses.

The strengths of our study are the longitudinal design and the large cohort (considering the rarity of OA) followed in a highly structured follow-up programme. Still, some limitations of our study should be addressed. First, not all children appeared at all scheduled visits to the outpatient clinic, resulting in missing data for these visits. With linear mixed models, we accounted for these missing data. Second, the overall nutritional intake of the children is unknown because a dietitian was not structurally involved in the follow-up programme. Finally, dietary management, GOR diagnostics/therapy, motility studies and use of antibiotics were not recorded prospectively. To our knowledge, there is no literature on the effect of poor gastrointestinal motility on growth in patients with OA. It would be interesting to correlate motility and growth in future studies in patients with OA.

In conclusion, we found physical growth in patients with OA to be compromised during the first 5 or 8 years of life. Still, at 12 years of age, growth parameters had improved to normal values in most children, but children who underwent fundoplication surgery had SDS-HFA and SDS-DTH significantly below SDS=0 at 12 years FIGURE 2.2 . The question is whether growth remains normal during puberty or whether nutritional intervention is needed in adolescence. Therefore, structural follow-up of all patients with OA, especially those who underwent fundoplication surgery, should be considered up to adulthood. Dietitians, as part of a multidisciplinary team, should be involved during (initial) hospitalisation and follow-up to optimize nutritional status in early years, which is crucial for normal brain and immune system development. Future multicenter studies should focus on optimisation of nutritional intake and on the effects of growth problems on brain development and school performance in this population.

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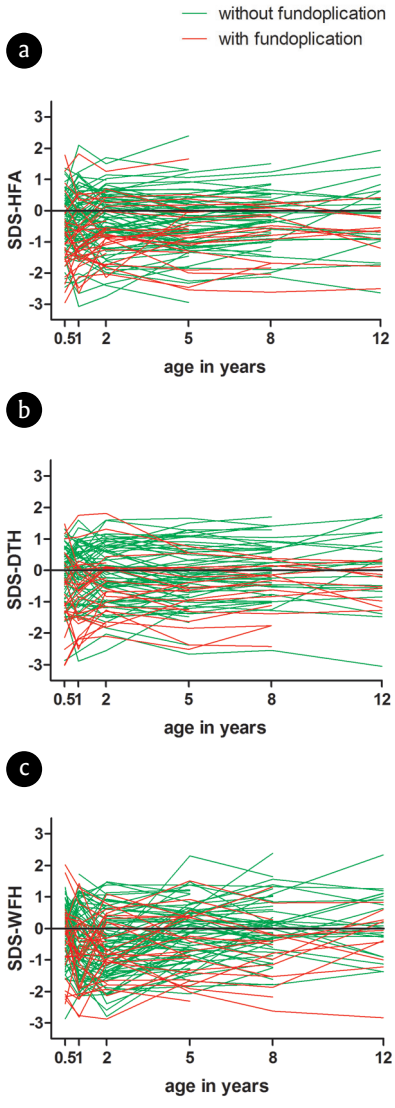
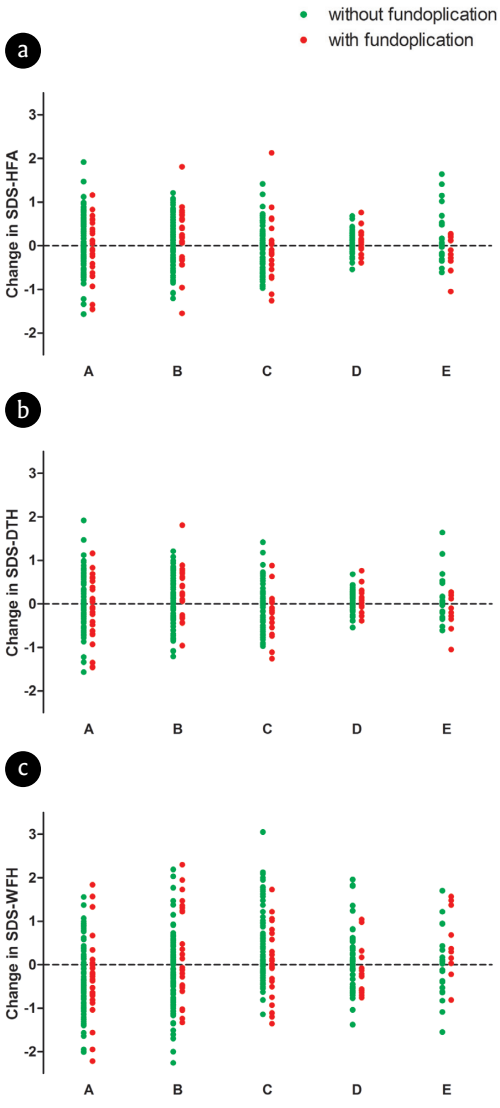
SUPPLEMENTARY MATERIAL

Supplementary table 2.1 Variation in age of all children attending visits

Routine visit	Age in years; median (IQR)
0.5 year visit	0.5 (0.5-0.6)
1 year visit	1.0 (1.0-1.1)
2 years visit	2.0 (2.0-2.1)
5 years visit	5.2 (5.1-5.5)
8 years visit	8.2 (8.1-8.3)
12 years visit	12.1 (12.0-12.2)



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

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ABSTRACT

Esophageal atresia (EA) is a rare congenital anomaly. Enhanced operative techniques and intensive care treatment have improved survival among children with repaired EA (range, 93-95%). Many (up to 67%) suffer from gastroesophageal reflux (GER). The high incidence of GER and improved survival among EA patients raises concerns about an increased risk of developing Barrett esophagus (BE) and esophageal cancer. This review provides an overview of the prevalence of esophagitis, BE, and esophageal cancer in EA patients and outlines suggestions for future research. A literature search indeed revealed a higher prevalence of BE in EA patients than in the generalized population and that this condition occurs at a much younger age. It should be noted that in some studies gastric metaplasia without intestinal metaplasia is defined as BE. Gastric-type mucosa in columnar-lined esophagus is probably of less clinical importance in terms of the likelihood of malignant transformation. Its inclusion therefore confounds the risk of esophageal adenocarcinoma. A total of eight cases of esophageal carcinoma at a young age, either squamous cell carcinoma or adenocarcinoma, have been reported. These observations bear important implications prompting for early onset lifelong BE/esophageal cancer surveillance to facilitate the diagnosis of (pre)neoplastic changes and early treatment.

INTRODUCTION

Esophageal atresia (EA) with or without tracheoesophageal fistula (TEF) is a rare anatomical anomaly, with a prevalence of 2.55 per 10,000 pregnancies in Europe [1]. Advancements in surgery and modern intensive care have led to survival rates up to 93 to 95% in dedicated centers, and more children nowadays reach adulthood [2, 3].

After surgical repair, many EA patients experience gastroesophageal reflux (GER) [4-8]. If untreated, chronic GER may lead to esophagitis, anastomotic strictures, metaplastic epithelial changes (gastric metaplasia or intestinal metaplasia), and esophageal adenocarcinoma (EAC). When the squamous mucosa in the distal esophagus is damaged, usually by GER, it is replaced by metaplastic columnar mucosa, so-called Barrett esophagus (BE). A study has suggested that metaplasia is found in approximately 42% of EA patients [9]. In case intestinal metaplasia is present in the metaplastic columnar mucosa, BE becomes an important risk factor for developing EAC, with an estimated incidence rate of 0.5% per year during follow-up [10]. In the general population, BE is reported in 1.6% of adults and is predominantly diagnosed in middle-aged white males [11]. It is suggested that the prevalence of BE in EA patients is higher and that it occurs at a much younger age [7]. Cancer in the upper gastrointestinal tract in EA patients has been described in 10 cases, of which 8 were esophageal carcinoma TABLE 3.1 and 2 squamous cell carcinoma not related to the native esophagus (related to the lung and to a subcutaneous skin tube reconstruction) [12-18].

Given the high prevalence of BE, the early development of esophageal cancer, and the possible absence of alarm symptoms in EA patients, surveillance programs seem warranted. Prospective long-term follow-up cohort studies, including endoscopic data of adult EA patients, are limited and guidelines for follow-up are lacking. The aim of this review is to give an overview of the prevalence of esophagitis, BE, and esophageal cancer in EA patients and outline suggestions for future research.

Gastroesophageal reflux

Gastroesophageal reflux disease (GERD) is considered a motility disorder, with transient lower esophageal sphincter relaxations as its main underlying mechanism in healthy premature infants, healthy adults, GERD patients, and EA patients (shortly after primary anastomosis and in adulthood) [19]. In EA patients several anatomic and functional causes can explain the increased occurrence of GER.

First, by pulling the distal esophagus more cranial during atresia repair the lower esophageal sphincter is displaced, resulting in sphincter incompetence and an increase in retrograde movements of gastric contents into the esophagus. The altered angle of His of the stomach fails to prevent GER [20, 21]. Second, surgical injury to the vagal nerve leads to dysmotility, and despite careful connection of the different muscle layers the esophageal peristaltic wave is disrupted at the anastomosis [19, 20]. Third, disturbed motility seems to be present before atresia repair as a result of deficient extrinsic and intrinsic innervation [19, 20]. Finally, delayed gastric emptying in EA patients and upper airway obstruction in EA patients with tracheomalacia or tracheal stenosis can also facilitate GER [19, 20].

Table 3.1 Reported esophageal cancer in EA patients (n=8)

References	Gender, age, type of EA, type of surgery	Type and location of esophageal cancer
Adzick et al. (1989) [14]	Female, 20 years Gross type C, primary repair	EAC, at GEJ with extension to lower esophagus and cardia
Deurloo et al. (2001) [12]	Male, 38 years Gross type C, primary repair	ESCC, at 2cm distal of the anastomosis
Alfaro et al. (2005) [15]	Female, 46 years Gross type E, primary TEF repair	EAC, in BE (18-35 cm)
Pultrum et al. (2005) [16]	Female, 22 years Gross type C, primary repair (high tension with post-operative mediastinal leakage and mediastinitis)	EAC, at anastomosis
Jayasekera et al. (2012) [13]	Female, 44 years Gross type C, primary repair	ESCC, at anastomosis (23cm) with metastasis in frontal lobe and mediastinum
Jayasekera et al. (2012) [13]	Female, 46 years Gross type C, primary repair	ESCC, mid-esophageal at 20-28 cm with reactive mediastinal and subcardinal lymph nodes
Jayasekera et al. (2012) [13]	Male, 46 years Gross type C, delayed primary repair (day 49)	ESCC, in BE (19-21 cm) with reactive para-aortic lymph node
Jayasekera et al. (2012) [13]	Male, 44 years Gross type C, primary repair, recurrent TEF	ESCC, tumor mass eroding through sternum and ribs

BE: Barrett's esophagus, EA: esophageal atresia, EAC: esophageal adenocarcinoma, ESCC: esophageal squamous cell carcinoma, GEJ: gastroesophageal junction, GER: gastroesophageal reflux, GERD: gastroesophageal reflux disease, TEF: tracheoesophageal fistula

GERD	Postsurgical esophageal stenosis and dilatations	Esophagitis and Barrett's esophagus	Habits of alcohol and smoking
No	Yes, multiple dilatations	No	No
Not reported	Yes, no dilatation possible, resection of stenosis	Not reported	Alcohol and smoking
Since age of 5 years	Yes, multiple dilatations	BE	No
Hiatus hernia with GER and aspirations Gastrostomy at age of 3 years and Nissen fundoplication at age of 16 years	Yes, multiple dilatations	Esophagitis	Not reported
Yes	No	Esophagitis	Smoking at age 15-19 years
Not reported	Yes, multiple dilatations	Not reported	No
Hiatus hernia with GER and aspirations Gastrostomy at age of 1 year and Allison repair at age 4 years	Yes, twice resection of stenosis and multiple dilatations	Esophagitis and a 16cm long BE with low grade dysplasia	Alcohol and smoking
Not reported	Yes, resection of stenosis, multiple dilatations	Not reported	Not reported

The reported prevalence of GER in EA patients after neonatal repair ranges from 32.8 to 54.2% during infancy and childhood, and from 5.9 to 66.7% during adolescence and adulthood TABLE 3.2 [4, 6-9, 22-39]. These wide ranges are probably explained by the different definitions used. A recent systematic review on long-term problems in EA patients found a high prevalence of GER, based on GER symptoms, of 40.2% compared with 10 to 20% in the general adult Western population [40, 41]. Typical symptoms of GER are heartburn and acid regurgitation, which are reported by 7.7 to 27% and 6.3 to 16%, respectively, of the general Western population [41]. In EA patients, the prevalence of these symptoms ranges from 14 to 38% and 7 to 34%, respectively [28, 38]. Dysphagia is present in 50.3% of the patients [40]. GER symptoms are not well correlated with the severity of esophageal damage: up to two-thirds of the patients with GER-related symptoms do not have mucosal erosions [42]. Most EA patients do not recognize GER symptoms as troublesome, as they have had these for years, resulting in chronic esophageal injury such as erosions, ulcerations, anastomotic strictures, BE, and eventually EAC.

The gold standard for diagnosing GER is ambulatory pH monitoring, completed with impedance. During pH monitoring acid reflux is measured, while esophageal impedance can also identify nonacid reflux. At endoscopy typical reflux-induced erosions can be observed. However, as mentioned above, not all patients with GER have mucosal damage, resulting in a low sensitivity of endoscopy as a diagnostic tool for GER [42, 43]. Also, esophageal biopsies, for assessment of histological changes and number of eosinophils, have not been proven to be useful, because of their low sensitivity and specificity and overlap with eosinophilic esophagitis and various other esophageal diseases (eosinophilic gastrointestinal diseases, celiac disease, drug hypersensitivity, and infection) [43, 44]. The basal zone normally compromises no more than 15% of the total epithelial thickness, the papillae reach up till two-thirds of the normal epithelium, and the maximum number of eosinophils in a normal esophageal biopsy specimen is 15 per high-power field [44, 45]. Eosinophilic esophagitis is characterized by eosinophilia, eosinophilic microabscesses, degranulated eosinophilia, basal cell hyperplasia, elongated rete pegs, and dilated intercellular spaces, but also in GERD patients and even in healthy individuals basal cell hyperplasia, elongated rete pegs, and eosinophilia can be found [46]. Therefore, histological assessment is often not conclusive to discriminate between the various esophageal diseases [43].

Treatment options for GERD are lifestyle modification, acid suppression and surgery. In view of the high occurrence of (severe) GER in EA patients, most newborns with EA receive medical therapy directly after birth. Medical treatment is often successful by reducing gastrointestinal and respiratory symptoms, but antireflux surgery, such as Nissen fundoplication, is still needed in up to 44% of the cases TABLE 3.2 [4, 6-8, 24-27, 29, 30, 32, 34-37, 39, 47]. The wrap fails in many patients. A review of 2013 reported a redo-fundoplication rate of 18% in EA patients, a much higher percentage than the 7% in GERD patients in the general population [20]. Another study

found an ever higher percentage of redo-Nissen procedures of 25% [48]. The modified anatomy in EA patients and the persistent dysmotility after medical or surgical anti-GERD treatment may explain the high occurrence of wrap failures [20, 49].

Abnormal reflux of gastric contents into the esophagus (and beyond) can cause serious esophageal problems (inflammation, erosions, ulcerations, anastomotic strictures, BE, and EAC) and pulmonary problems (asthmatic complaints, inflammation, and respiratory distress of apparent life-threatening events). The disturbed esophageal motility in EA patients reduces acid clearance and increases the adverse effects of GER in this population. Early diagnosis and treatment of GER in EA patients may influence the onset of GER-related complications.

Esophagitis

Chronic GER may lead to esophagitis with mucosal breaks, especially when untreated. Upper endoscopy is the most sensitive diagnostic tool for assessment of GER-related mucosal injury. During upper endoscopy, esophagitis is classified using the Los Angeles Classification [50]. For histological examination, the Ismail-criteria have long been considered one of the most reliable criteria for diagnosing reflux esophagitis and these are still used [45]. Although histology can be useful to assess the individual therapeutic response in GERD, routine biopsies cannot be recommended as a diagnostic tool for GERD as the correlation between histological findings and GERD in the absence of mucosal lesions is poor [43].

In EA patients, the prevalence of esophagitis observed during an endoscopy is considerably higher than that in the general population: 25.1 versus 12 to 15% TABLE 3.2 [6, 7, 22, 24, 27-32, 35, 36, 38, 39, 51, 52]. An endoscopic diagnosis of erosive esophagitis is made in 31.5% of the infants and children with EA, with histology revealing moderate-to-severe esophagitis in 8.5% TABLE 3.2 [22, 24, 27]. In adolescents and adults with EA, esophagitis is observed during endoscopic and histological evaluation in 26.4 and 20%, respectively TABLE 3.2 [6, 7, 28-32]. A recent systematic review found a prevalence of histological esophagitis of 56.5% in EA patients [40]. This can hardly be interpreted as mild inflammation, as findings included minimal basal hyperplasia, subtle reactive changes, and slight amounts of lymphocytic, eosinophilic, and neutrophilic infiltration in the epithelium, which are also present in healthy individuals [43, 46].

Table 3.2 Literature reports on the prevalence of GER symptoms, pH-measurements, esophagitis, gastric metaplasia, Barrett's esophagus and fundoplication surgery in EA patients: children(A), adults (B) and both children and adults (C)

A Studies in children

References	Age in years	Symptoms of GER (chest pain, pyrosis, regurgitation)	Pathological GER at pH-measurement	Endoscopic esophagitis (with erosions)
	median (range)	n/N (%)	n/N (%)	n/N (%)
Pedersen et al. (2013) [22]	10.3 (7.1-13.3)	33/59 (55.9)	32/59 (54.2)	29/59 (49.2)
Catalano et al. (2011) [23]	1.3 (0.3-3.3)	14/22 (63.6)	10/22 (45.5)	NR
Castilloux et al. (2010) [24]	7.3 (0.4-17.9)	28/45 (62.2)	9/24 (37.5)	3/45 (6.7) [b]
Kawahara et al. (2009) [25]	0.1 (0.1-0.3)	NR	8/16 (50.0)	NR
Koivusalo et al. (2007) [26]	0.5	NR	10/61 (16.4) [e,f]	NR
	1		20/61 (32.8) [e,f]	
	3			
	5			
	10			
Deurloo et al. (2002) [4]	0.25	NR	53/128 (41.4)	NR
Lindahl et al. (1993) [27]	7.6 (2-11)	NR	NR	20/39 (51.3)
Total number		**75/126 (59.5)**	**112/249 (45)**	**45/143 (31.5)**

B Studies in adults

References	Age in years	Symptoms of GER (chest pain, pyrosis, regurgitation)	Pathological GER at pH-measurement	Endoscopic esophagitis (with erosions)
	median (range)	n/N (%)	n/N (%)	n/N (%)
Gatzinsky et al. (2015) [28]	31 (25-40)	11/29 (37.9)	2/15 (13.3)	10/24 (41.7)
Huynh-Trudeau et al. (2015) [29]	25 (18-44)	12/41 (29.3)	NR	6/32 (18.8)
Sistonen et al. (2010) [6]	36 (22-57)	34/101 (33.7)	NR	8/58 (13.8)
Deurloo et al. (2008) [30]	28.5 (18-42)	7/21 (33.3)	3/21 (14.3)	3/21 (14.3)
Taylor et al. (2007) [7]	33 (20-48)	83/132 (62.9)	NR	36/62 (58.1)
Deurloo et al. (2003) [32]	34 (28-45)	20/38 (52.6)	NR	2/23 (8.7)
Krug et al. (1999) [31]	? (18-26)	13/39 (33.3)	NR	2/34 (5.9)
Biller et al. (1987) [8]	26 (22-31)	9/12 (75)	6/9 (66.7)	NR
Total number		**189/413 (45.8)**	**11/45 (24.4)**	**67/254 (26.4)**

Histological esophagitis (moderate-severe)	Gastric metaplasia in distal esophagus	Barrett's esophagus (intestinal metaplasia)	Fundoplication surgery	Total number of GERD diagnosis according to ACG guidelines [a]
n/N (%)	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**
0/59 (0)	0/59 (0)	1/59 (1.7)	NR	32/59 (54.2)
NR	NR	NR	NR	10/22 (45.5)
5/45 (11.1) [c]	16/45 (35.6)	0/45 (0)	20/45 (44.4)	20/45 (44.4)
NR	NR	NR	4/17 (23.5)	8/16 (50.0)
-	0/61 (0)	0/61 (0)	18/61 (29.5)	20/61 (32.8) [d]
24/61 (39.3) [e,f]				
23/52 (44.2) [e,f]				
22/43 (51.2) [e,f]				
12/27 (44.4) [e,f]				
NR	NR	NR	41/128 (32.0)	53/128 (41.4)
7/37 (18.9)	3/37 (8.1)	0/39 (0)	9/39 (23.1)	
12/141 (8.5)	**19/202 (9.4)**	**1/204 (0.0)**	**92/290 (31.7)**	**163/370 (44.1)**

Histological esophagitis (moderate-severe)	Gastric metaplasia in distal esophagus	Barrett's esophagus (intestinal metaplasia)	Fundoplication surgery	Total number of GERD diagnosis according to ACG guidelines [a]
n/N (%)	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**
11/24 (45.8)	NR	2/24 (8.3)	NR	10/24 (41.7)
8/12 (75) [e,g]	6/32 (18.8) [g]	4/32 (12.5) [g]	15/41 (36.6)	15/41 (36.6)
3/101 (3.0)	15/101 (14.9)	6/101 (5.9)	10/101 (9.9)	8/58 (13.8)
8/19 (42.1)	NR	NR	2/25 (8.0)	3/21 (14.3)
NR	0/62 (0)	7/62 (11.3)	14/132 (10.6)	36/62 (58.1)
11/21 (52.4)	0/21 (0)	1/21 (4.8)	1/40 (2.5)	2/23 (8.7)
7/17 (41.2) [e,h]	0/17 (0) [e,h]	2/17 (11.8) [e,h]	NR	2/34 (5.9)
NR	0/12 (0)	1/12 (8.3)	2/12 (16.7)	6/9 (66.7)
33/165 (20)	**21/228 (9.2)**	**21/252 (8.3)**	**44/351 (12.5)**	**82/272 (30.1)**

C Studies in children and adults

References	Age in years	Symptoms of GER (chest pain, pyrosis, regurgitation)	Pathological GER at pH-measurement	Endoscopic esophagitis (with erosions)
	median (range)	n/N (%)	n/N (%)	n/N (%)
Koivusalo et al. (2013) [34]	8.8 (0.1-21) 1	NR	NR	NR
Schneider et al. (2013) [9]	16.6 (15-19)	NR	NR	NR
Burjonrappa et al. (2011) [35]	6.6 (0.6-19)	NR	21/33 (63.6)	4/38 (10.5)
Deurloo et al. (2005) [36]	17 (10-26)	28/86 (32.6)	NR	13/49 (26.5)
Schalamon et al. (2003) [37]	10.3 (0.5-19.1)	NR	NR	NR
Tomaselli et al. (2003) [38]	15.8 (7-28)	13/26 (50)	2/12 (16.7)	3/15 (20)
Somppi et al. (1998) [39]	12.6 (3.5-30)	8/43 (18.6)	9/41 (22.0)	1/31 (3.2)
Tovar et al. (1995) [33]	17.1 (9-26)	13/22 (59.1) [i]	12/22 (54.5) [i]	NR
Total number		**326/716 (45.5)**	**167/402 (41.5)**	**133/530 (25.1)**

EA: esophageal atresia, GER: gastroesophageal reflux, GERD: gastroesophageal reflux disease, NR: not (clearly) reported

a GERD diagnosis defined as: fundoplication surgery performed, pH-measurement positive or endoscopic esophagitis (according to the ACG guidelines) [43].

b No official classification used for endoscopic grading of esophagitis.

c Histological diagnosis of three biopsies was unspecified.

d Fundoplication surgery and pH-measurement.

e To exclude selection bias, these numbers are not used to calculate the total prevalence of the features, see below the different reasons.

f Fundoplication surgery, pH-measurement, and histological esophagitis (moderate-to-severe).

g Biopsies (n = 12) taken in presence of endoscopic abnormalities: Barrett esophagus (n = 10) and/or esophagitis (n = 6).

h Biopsies (n = 17) taken in presence of esophagitis and/or Barrett epithelium (n = 8) or normal mucosa (n = 9).

i Patients with a history of fundoplication surgery or severe/obvious symptoms were excluded from this study.

Histological esophagitis (moderate-severe)	**Gastric metaplasia in distal esophagus**	**Barrett's esophagus (intestinal metaplasia)**	**Fundoplication surgery**	**Total number of GERD diagnosis according to ACG guidelines** [a]
n/N (%)	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**
-	NR	NR	37/130 (28.5)	37/130 (28.5)
62/130 (47.7) [e,f]				
NR	36/88 (40.9)	1/88 (1.1)	NR	no valuable data
NR	11/38 (28.9)	1/38 (2.6)	17/51 (33.3)	21/33 (63.6)
15/40 (37.5)	3/40 (7.5)	0/40 (0)	19/92 (20.7)	13/49 (26.5)
10/74 (13.5)	13/74 (17.6)	0/74 (0)	21/74 (28.4)	21/74 (28.4)
NR	NR	NR	NR	3/15 (20)
7/35 (20)	2/35 (5.7)	0/35 (0)	5/52 (9.6)	9/41 (22.0)
NR	NR	NR	0/22 (0) [e,i]	12/22 (54.5) [e]
77/455 (16.9)	**105/695 (15.1)**	**24/731 (3.3)**	**235/1040 (22.6)**	**360/1006 (35.8)**

Barrett esophagus

The diagnosis BE is made if normal squamous epithelium of the distal esophagus has been replaced by metaplastic columnar mucosa [10, 53, 54]. Three types of esophageal metaplastic columnar epithelium are distinguished: gastric fundic type epithelium (surface mucus, parietal, and chief cells), gastric cardiac type epithelium (mucus secreting cells), and intestinal type epithelium (goblet cells) [55]. Intestinal metaplasia is the most biologically unstable type of metaplastic columnar epithelium with the greatest risk of neoplastic progression through dysplasia to adenocarcinoma [54]. The annual incidence of EAC in BE patients, defined as the presence of columnar-lined esophagus with intestinal metaplasia, is 0.5% [10]. Whether gastric metaplasia (fundic or cardiac type epithelium) is associated with malignant transformation remains unclear [27, 36, 39, 56]. Importantly, the definition of BE differs between guidelines in respect of whether or not intestinal metaplasia is present [10, 53, 54].

The estimated prevalence of BE in the general population is 1.6% [11]. In EA patients, the prevalence of BE varies between 0 and 12.5% and that of gastric metaplasia between 0 and 40.9% TABLE 3.2 [6-9, 22, 24, 26-29, 32, 35-37, 39]. The great variety in BE prevalence in EA patients can be ascribed to different definitions used. It should be noted that in several studies gastric metaplasia without intestinal metaplasia also is defined as BE. This illustrates the importance of using a uniform working definition of BE, so as to prevent overdiagnosis and overtreatment. While in the general population BE patients are usually middle-aged white males, in EA patients BE is diagnosed at a remarkably younger age. In a study from Taylor et al, BE was diagnosed in 7/62 (11.3%) patients with a median age of 37 years (range, 21–43 years) [7]. There is some evidence that EA patients with TEF recurrence, long gap EA, esophageal stricture resection in childhood, esophageal stricture present in adulthood, severe reflux symptoms, and age above 30 years are at an increased risk for developing BE [6, 7].

To detect BE it is important to identify landmarks such as the Z-line (transition line of squamous to columnar epithelium) and the gastroesophageal junction (GEJ) [53]. Normally, the Z-line corresponds to the GEJ and is in line with the diaphragm. After EA repair, especially after a gastric pull-up, the GEJ is located proximal of the diaphragm. This modified anatomy may complicate landmark recognition.

The purpose of reducing acid exposure in BE is to prevent the development of high-grade dysplasia and EAC. Acid suppression drugs are prescribed in almost all BE patients for chemoprevention and symptom control. Antireflux surgery is not superior to medical therapy to prevent malignant progression of BE [10, 54]. Moreover, it does not fully protect GERD patients against BE development. Sistonen et al found that 40% of the EA patients with prior anti-reflux surgery developed esophageal gastric or intestinal metaplasia [6].

Endoscopic resection with or without ablation therapy can be offered with curative intent when BE with high-grade dysplasia or early stage esophageal cancer is detected. The treatment of choice depends on the tumor stage, patient's age, comorbidity, preferences, and local expertise [53, 54, 57-59].

Esophageal cancer

The two commonest types of esophageal cancer are EAC deriving from the columnar mucosa and esophageal squamous cell carcinoma (ESCC) originating from the squamous mucosa. Dysphagia is often the first symptom of esophageal cancer. However, dysphagia is common in EA patients (prevalence 48-72%) and patients therefore are not necessarily alarmed by this symptom [5]. Because of the association between BE and EAC, EA patients with prolonged GER and BE may have an increased risk for malignant progression.

Over the last decades, survival of EA patients has increased and many more patients reach adulthood. Long-term follow-up studies in adult EA patients are scarce. To date, eight cases of esophageal cancer in adult EA patients have been reported: three EAC and five ESCC TABLE 3.1 [12-16]. The tumors were mainly located in the middle esophagus and diagnosed at a young age (median, 38 years; range, 20-46 years). A few articles about cancer risk in this population have been published, but large follow-up cohort studies in patients throughout adolescence and adult life are needed for proper risk assessment and stratification. Two Scandinavian studies, both found three cases of cancer (no esophageal cancer) in a cohort of 870 and a cohort of 272 EA patients, respectively [60, 61]. The esophageal cancer prevalence was not higher than in the general population, but the median follow-up in both studies was only 16 and 35 years, respectively. In an Australian cohort of 309 adult EA patients (age ≥40 years), of whom 76 underwent endoscopic screening, 4 ESCC were found [13]. However, the cause of death or long-term outcome was not known in 120 of the 309 patients (38.8%). The cumulative incidence of ESCC in EA adults above 40 years of age was 50-fold higher than that in the general population.

These findings should be interpreted with caution, however because of the small power of the studies and the relatively short follow-up period. To date the relevant literature has reported more ESCC than EAC. Possible reasons are the fact that EA patients have a higher risk of developing ESCC than EAC, publication bias, or a relatively short follow-up in adulthood. With regard to the latter, EAC derived from BE could develop on a longer term than ESCC. The follow-up period in most of the studies, including EA patients is relatively short.

Screening and surveillance

As described above, EA patients appear to have a higher prevalence of BE at a younger age compared with the general population. Due to the poor prognosis of patients with esophageal cancer, early diagnosis is of utmost importance to make curative and less invasive treatment still feasible. For recommendations about endoscopic screening and surveillance of BE in EA patients, presence of intestinal metaplasia should be taken into account as gastric type mucosa in columnar-lined esophagus is of less clinical importance in terms of the likelihood of malignant transformation.

To date guidelines on esophageal follow-up on EA patients are lacking. Several screening strategies have been suggested as a clinical screening in all patients aged 15 to 25 years, with endoscopy performed if any GER symptoms are present [7]. Another study suggested endoscopic surveillance at the ages of 15, 30, 40, 50, and 60 years, with intensification of this protocol if pathological observations are made: yearly in case of BE and 5-yearly in the presence of esophagitis, gastric metaplasia, severe esophageal strictures, recurrent TEF, severe GER symptoms, or the need for continuous anti-GERD medication [5]. Other endoscopy protocols suggest screening in all adults, from the age of 30 years for patients with significant primary surgery complications; from the age of 20 years, regardless of symptoms (5-yearly until the age of 30 years, 3-yearly until the age of 40 years, 2-yearly after 40 years of age); and screening once before adulthood with surveillance through adulthood with 5 to 10 year intervals (3-yearly in case of BE or twice a year with dysplasia) [6, 9, 13, 31].

Future prospects

Large cohort studies with longer follow-up focusing on the development of BE and esophageal cancer in EA patients are scarce. A few suggestions for endoscopic surveillance programs in this population have been put forward, but none of these strategies have been validated in a population-based follow-up study. Screening all adult EA patients is labor intensive. Moreover, the inconvenience and burden of repeated endoscopies for the patients should not be underestimated. Future large prospective follow-up cohort studies are needed to define the actual BE and cancer risk in (adult) EA patients. In this regard, it is important to identify pivotal risk factors, including genetic predisposition, to focus and intensify surveillance in those patients at true risk for developing EAC or ESCC, rendering surveillance program more cost-effective and less inconvenient for EA patients overall.

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4

Evaluation of gastroesophageal reflux in children born with esophageal atresia using pH and impedance monitoring

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ABSTRACTS

Objective

To evaluate acid and non-acid gastroesophageal reflux in infants and school-aged children with esophageal atresia (EA) using pH-impedance (pH-MII) monitoring.

Methods

Between 2012-2017, all 24-hour pH-MII studies performed in infants (≤18 months) and 8-year olds with EA were included. Anti-acid therapy was discontinued before study. Exclusion criteria were: isolated tracheoesophageal fistula; esophageal replacement therapy; tube feeding; and monitoring <18 hours. Automatically detected retrograde bolus movements (RBM) were manually reviewed and modified/deleted if necessary.

Results

We included 57 children (51% male; 2% isolated EA; 44% thoracoscopic EA repair): 24 infants (median age 0.6 years) and 33 school-aged children (median age 8.2 years). Of the automatically detected 3,313 RBM, 1,292 were manually deleted from the tracings: 52% of non-acid RBM and 8% of acid RBM (mainly misinterpreted swallows or one event recognized as several events). In infants, median reflux index (RI; pH<4) was 2.6% (abnormal in n=2), median RBM was 61 (62% non-acid, 58% mixed) and median of the mean BCT was 11 seconds. In older children, median RI was 0.3% (abnormal in n=4), median RBM was 21 (64% non-acid; 75% mixed) and median of the mean BCT was 13 seconds.

Conclusions

Most children with EA off medication have a normal RI, yet experience a significant number of non-acid RBM. After manual revision of the tracings a high percentage of RBM was deleted. Our data show that automated impedance analysis software needs refinement for use in infants and children with EA and question the need for standard anti-acid therapy in these patients.

INTRODUCTION

Esophageal atresia (EA) with or without a tracheoesophageal fistula (TEF) is a relatively common birth defect in which the continuity of the esophagus is interrupted (European prevalence: 2.43 per 10,000 births) [1]. As a result of inborn deficient esophageal innervation and surgical nerve injury, EA patients suffer from esophageal dysmotility [2, 3]. Gastroesophageal reflux (GER; acid and non-acid) is a physiologic phenomenon. When GER causes troublesome symptoms interfering with daily life or complications it is referred to as GER disease (GERD) [4]. GERD is thought to be common after surgical EA repair in both children and adults [5, 6]. It results in respiratory and gastrointestinal problems in the short-term (e.g. aspiration pneumonia, apparent life-threatening events, dysphagia, feeding problems) and long-term (e.g. chronic respiratory symptoms, esophagitis, esophageal strictures, Barrett's esophagus, esophageal cancer) [6-10]. Given the high prevalence of GERD in children with EA (up to 54% in some studies), it is important to diagnose and manage GERD to reduce associated complications [5, 6].

Although many children with EA are exposed to chronic GER, only a few experience troublesome symptoms. Results from pH-impedance (pH-MII) studies as well as endoscopic evaluations in children with EA show that asymptomatic children can have severe abnormalities [11-14]. Therefore, the ESPGHAN-NASPGHAN Guideline (2016) recommends to routinely prescribe proton pump inhibitors (PPI) for the first year of life and monitor GER using pH-MII monitoring and/or endoscopy at time of discontinuation (regardless of symptoms) and during long-term follow-up in symptomatic children with EA [6].

We hypothesized that GER occurs frequently in children with EA, not only in infancy but even thereafter. Moreover, based on clinical interpretation of several pH-MII studies prior to this study we assumed that disturbed impedance patterns in EA patients leads to over-detection of reflux events in automated analysis. We aimed to evaluate and characterize acid and non-acid GER in infants and school-aged children with EA using pH-MII monitoring and to evaluate the rate of over-detection by automated software in this specific population.

MATERIALS AND METHODS

Patients

All children with EA born in our hospital are offered a 24-hour pH-MII study at the age of 0.5 and 8 years as part of a longitudinal multidisciplinary follow-up program [15]. As standard of care, all children receive PPI for at least six months after surgical EA repair. We retrospectively reviewed all pH-MII studies conducted in children with EA between September 2012 and October 2017. Exclusion criteria were: isolated TEF; esophageal replacement therapy (e.g. gastric pull-up, jejunal/colonic interposition); use of tube feeding; and pH-MII study duration <18 hours. The Medical Research Involving Human Subjects Act was considered not applicable to the study protocol (protocol ID MEC-2017-185).

Data collection

Data retrieved from patient records included baseline characteristics (e.g. gender, gestational age, type of EA, type of EA repair) and clinical data at time of pH-MII monitoring (e.g. symptoms, use of anti-reflux medication, z-scores height and weight-for-height) [16, 17]. All 8-year old children were asked to fill in an online validated questionnaire for detecting GERD by Manterola et al. [18, 19]. A cut-off score >3 was used.

Small for gestational age was defined as a birth weight two standard deviations (SD) below normal. Prematurity was defined as gestational age <37 weeks. Pulmonary infections were defined as lower respiratory tract infections requiring antibiotic therapy and/or hospital admission.

pH-MII monitoring protocol

Children were intubated with an age appropriate pH-MII catheter. We used two available types of pH-MII catheters to perform 24-hour pH-MII studies: Greenfield (Dover, USA) single use antimony pH-MII catheters (6.4 French, 6 impedance channels, 1-2 pH channels) and Laborie ion-sensitive field-effect transistor (ISFET) disposable pH-MII catheters (6 French, 6 impedance channels, 1 pH channel). A chest x-ray was performed to ensure correct pH channel position (three vertebrae above the diaphragm) [20]. All anti-acid and prokinetic therapy was discontinued prior to the start of the pH-MII assessment (five and two days, respectively). Parents were asked to fill in a diary during pH-MII monitoring to monitor symptoms, body position and intake of food and beverages. Patients were instructed not to eat acid foods or drink carbonated beverages.

Manual correction of reflux events

Initial manual review was performed to ensure correct diary records and to delete artefacts. Then MMS database software 9.5 (Medical Measurement Systems B.V., Enschede, The Netherlands) was used for automated analysis (acid/alkaline limits: pH 4.0 and 7.0; minimum reflux duration pH- and MII-results: 5 seconds; air threshold: 5000Ω). All reflux events – identified as such by the software – were manually reviewed and modified (duration; number of impedance channels involved; liquid/mixed reflux content) by one researcher unaware of the clinical symptoms (FV). A second reviewer (MvW) examined inconclusive events. RBM were deleted in case both reviewers agreed the RBM was misinterpreted by the software.

Data analysis

Parameters analyzed in this study included number of pH changes to <4; reflux index (RI; acid exposure index (%)); number of long (>5 minutes) acid exposures; longest acid exposure (minutes); number of retrograde bolus movements (RBM); number of acid/non-acid (pH ≥4) RBM; number of liquid/mixed RBM; mean bolus clearance time (BCT; seconds); number of proximal bolus exposures (reaching proximal impedance channel); symptom index for reflux (SI); and symptom association probability (SAP)(window of 120 seconds before and after a reflux event). A RI>7% was considered to be abnormal, <3% to be normal, and 3%-7% to be indeterminate [21]. SI≥50% and SAP≥95% were considered positive [22].

Data are presented as frequencies, mean (SD) or median (minimum; maximum; inter-quartile range (IQR)). Data were analyzed with SPSS 21.0 (SPSS Inc., Chicago, IL) using descriptive statistics. Non-parametric Mann-Whitney U test was used to compare continues variables and Pearson's chi-square test or Fisher's exact test for categorical variables. The two-tailed level of significance was set at p=0.05.

RESULTS

Demographics TABLE 4.1

Of the 69 children born between 2011-2017 (aged ≤18 months in study period), three children had died. Sixteen children fulfilled exclusion criteria, mainly because of tube feeding FIGURE 4.1. We included 24/50 (48.0%) eligible infants (median age 0.6 (range 0.2-1.5) years). Reasons for not being included are listed in FIGURE 4.1. Of the 74 children born between 2004-2009 (aged 8 years in study period), six children had died. Nine children fulfilled exclusion criteria. We included 33/59 (55.9%) children (median age 8.2 (range 8.0-9.0) years).

Table 4.1 Patient demographics (N=57)

	Age ≤18 months (N=24) n (%) / median (min; max; IQR)	**Age 8 years (N=33) n (%) / median (min; max; IQR)**
Male gender	14 (58.3)	15 (45.5)
Age (years)	0.6 (0.2; 1.5; 0.5-1.1)	8.2 (8.0; 9.0; 8.1-8.4)
Gestational age (weeks)	38.1 (30.4; 41.7; 35.3-40.0)	38.6 (28.9; 42.3; 37.0-40.1)
Prematurity	7 (29.2)	7 (21.2)
Birthweight (gram)	2595 (854; 3630; 1746-3078)	2850 (1080; 3810; 2235-3190)
Small for gestational age	4 (16.7)	4 (12.1)
Type of esophageal atresia		
– Gross type A	0	1 (3.0)
– Gross type C	24 (100.0)	31 (93.9)
– Gross type D	0	1 (3.0)
Type of esophageal correction		
– Primary anastomosis	23 (95.8)	30 (90.9)
– Delayed anastomosis	1 (4.2)	3 (9.1)
Type of surgery		
– Thoracoscopy	17 (70.8)	8 (24.2)
– Thoracotomy	6 (25.0)	25 (75.8)
– Converted	1 (4.2)	0
Z-score for weight-for-height; mean (SD)	-0.5 (1.1)	-0.3 (1.1)
Wasting (acute malnutrition)	2 (8.3)	2 (6.1)
Use of anti-reflux medication		
– Proton pump inhibitor	11 (45.8)	2 (6.1)
– H2 antagonist ± prokinetic drug	11 (45.8) [a]	0
– None	2 (8.3)	31 (93.9)
Pulmonary infections [b]	1 (4.2) [c]	8 (24.2) [d]
Prophylactic antibiotics (airways)	2 (8.3)	2 (6.1)
Symptoms		
– Gastrointestinal	2 (8.3) [e]	6 (18.2) [f]
– Respiratory	2 (8.3) [e]	2 (6.1) [f]
– None	20 (83.3)	25 (75.8)
Gastroesophageal reflux questionnaire (Manterola)	-	2 (0; 9; 1-4)
Nissen fundoplication surgery	0	8 (24.2) [g]

a Five children used Ranitidine and Domperidone.

b Defined as lower respiratory tract infections requiring antibiotics and/or hospital admission since birth (infants) or in the previous year (8-year olds).

c One infection in the previous year.

d One (n=4) and 2-4 (n=4) infections in the previous year.

e Vomiting unrelated to food intake/physical activity (n=1), frequent vomiting (n=1), ALTE (n=1), cough (n=1).

f Regurgitation (n=2), acidic reflux (n=1), nausea (n=1), nausea/abdominal pain (n=1), foetor ex ore and abdominal pain related to food intake (n=1), night cough (n=2).

g Median age of 5 (range 3-87) months at time of Nissen fundoplication.

Demographics of the 57 included children and the 52 non-included children did not significantly differ SUPPLEMENTARY TABLE 4.1 . In 43.9% of included children thoracoscopic EA repair was performed. Twenty-four children were using anti-reflux medication (91.7% of infants and 6.1% of older children), which was discontinued prior to pH-MII monitoring. Nissen fundoplication was previously performed in eight (24.2%) 8-year old children (median age 0.5 years).

pH-MII studies

Greenfield catheters were used in 30 (52.6%) and ISFET catheters in 27 (47.4%) of the 57 pH-MII studies. Of the 57 included pH-MII studies, we evaluated 52 complete pH-MII studies, three studies showed no reliable pH results due to pH-sensor malfunctioning and in two studies impedance results were not analyzed (after deleting artefacts, duration of the impedance tracing was <18 hours).

Manual correction of reflux events

In total 3,313 RBM were detected by MMS software of which 1,287 (39%) RBM were manually deleted from the tracings: 52% of all non-acid RBM (mainly swallows misinterpreted as being a RBM) and 8% of all acid RBM (mainly swallowing or a single event being recognized as several events by the software) SUPPLEMENTARY FIGURE 4.1 . Median RI was 2.6% in infants and 0.6% in older children. TABLE 4.2 shows all other pH-MII parameters.

In infants, pH results were abnormal in 2/22 (10%) evaluated pH studies; one of these had apparent life-threatening events suspected to be GER related. Indeterminate pH results were found in six (27%) infants, two of whom (33%) suffered from daily regurgitation/vomiting. Normal pH results were found in 14 (64%) infants, one was symptomatic (day and night cough). A median of 61 (range 0-134) RBM were observed. Four infants had >100 RBM/24 hours [22].

In older children, pH results were abnormal in 4/32 (12.5%) pH studies, three of them (75%) were symptomatic (regurgitation, acid reflux and night cough). None of the older children with abnormal pH results had undergone fundoplication surgery prior to the pH-MII study. Indeterminate pH results were found in two (6%) children, both asymptomatic, and pH results were normal in 26 (81%) children, five (19%) reported symptoms (regurgitation, nausea, nausea/abdominal pain, foetor ex ore/abdominal pain and night cough). A median of 21 (range 0-54) RBM were observed and none of the older children had >70 RBM/24 hours [22].

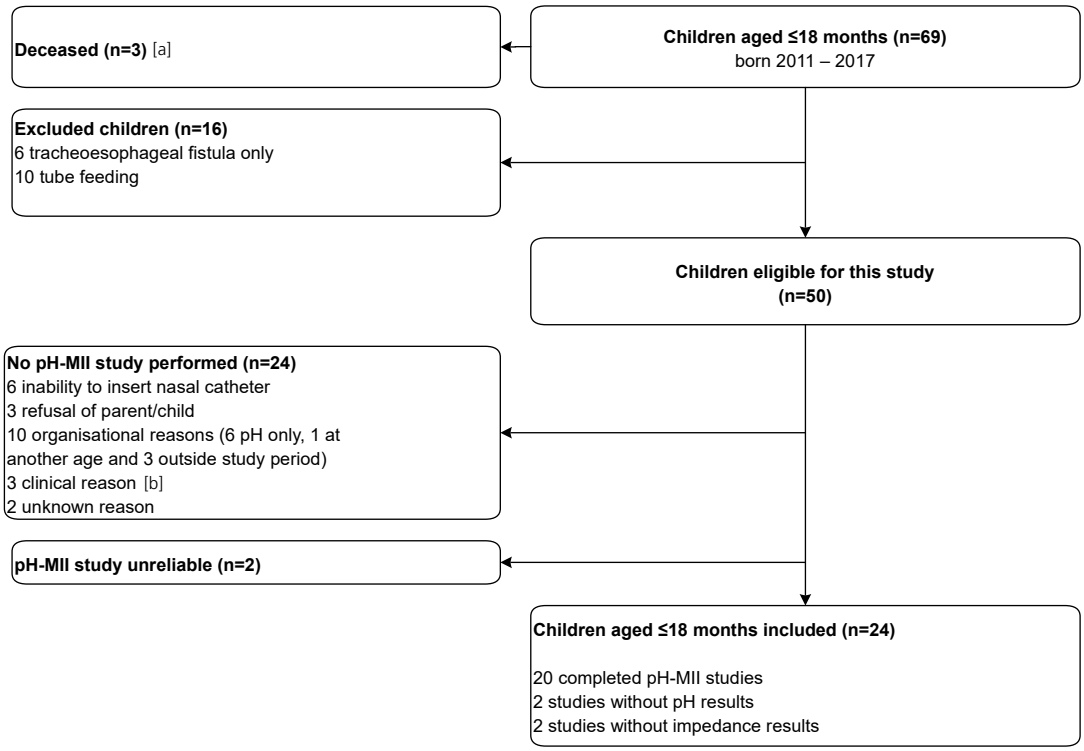

Figure 4.1 Flowchart of children included in study.

a Deceased at a median age of 71 (range 3-704) days. Causes: multiple major anomalies (n=5), recurrent sepsis (n=1), reanimation complicated with sepsis and severe neurological impairment (n=1), acute apparent life-threatening event based on intracerebral bleeding and ischemia (n=1), sudden death with unknown cause (n=1).

b Clinical reasons for absence of pH-MII studies: absence of symptoms after a recent Nissen fundoplication (n=1); normal esophagus observed at endoscopy in an asymptomatic child treated with anti-reflux medical therapy (n=1); and expectative management in a child with a short esophagus, intrathoracic stomach and proven gastroesophageal reflux (n=1).

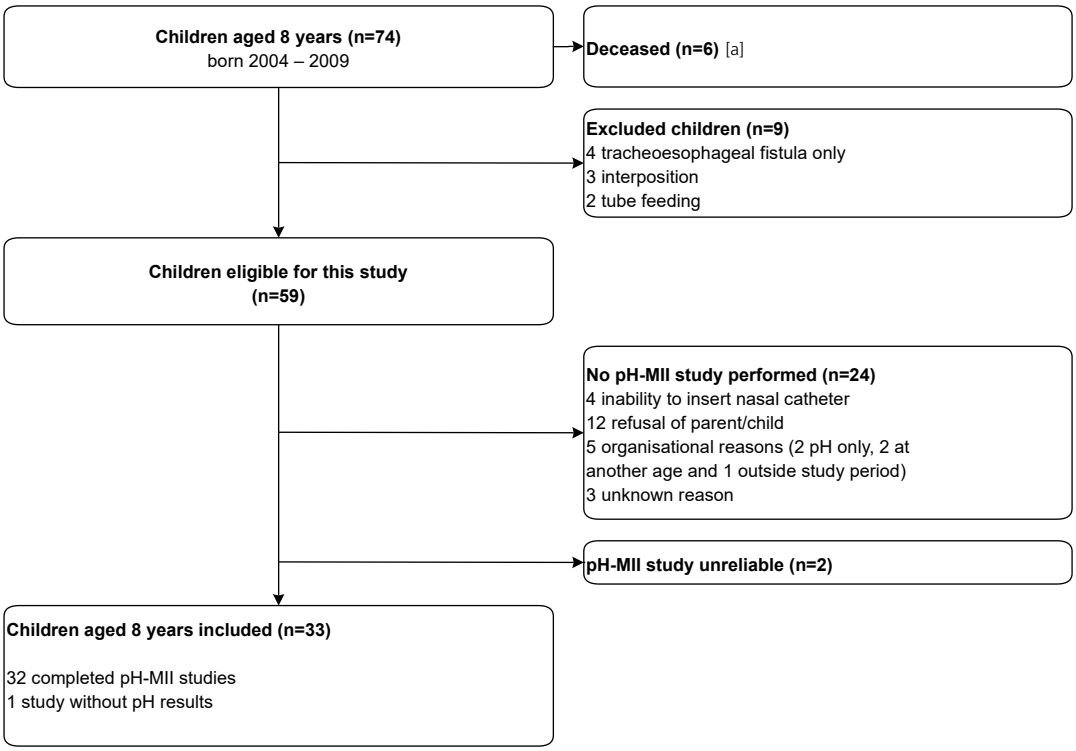

Table 4.2 Results from pH-impedance monitoring in children born with esophageal atresia after manual modification of reflux events

	Age ≤ 18 months (N=24) [a]			Age 8 years (N=33) [b]		
	n	median	min; max; IQR	n	median	min; max; IQR
Monitoring duration (min)	24	1369	1123; 1478; 1334-1407	33	1352	1230; 1511; 1331-1393
pH results						
– Number of acid exposures	22	35.0	4.0; 186.0; 17.5-68.5	32	7.5	0.0; 65.0; 2.0-17.8
– Reflux index (%)	22	2.6	0.1; 28.5; 1.1-4.6	32	0.3	0.0; 14.4; 0.1-2.5
– Number of long acid exposures	22	1.0	0.0; 11.0; 0.0-1.3	32	0.0	0.0; 8.0; 0.0-1.0
– Longest acid exposure (min)	22	6.0	0.4; 67.2; 3.3-10.0	32	2.2	0.0; 111.0; 0.6-8.4
Impedance results						
– Number of RBM	22	61.2	0.0; 133.7; 16.7-98.3	33	20.7	0.0; 53.7; 11.2-31.6
– Number of acid RBM	20	20.9	0.0; 85.6; 6.8-38.1	32	7.0	0.0; 45.7; 0.3-11.0
– Number of nonacid RBM	20	31.2	0.0; 73.1; 9.9-60.2	32	11.2	0.0; 36.3; 6.9-16.7
– Number of liquid RBM	22	21.1	0.0; 58.3; 5.5-50.0	33	4.2	0.0; 21.2; 2.2-11.8
– Number of mixed RBM	22	30.2	0.0; 92.0; 11.1-60.1	33	12.6	0.0; 44.6; 6.4-23.3
– Mean BCT (sec)	22	11.0	0.0; 13.0; 9.0-12.0	33	13.0	0.0; 18.0; 8.5-14.0
– Number of proximal bolus exposures	22	5.0	0.0; 80.2; 1.1-11.5	33	0.0	0.0; 8.7; 0.0-1.2

BCT: bolus clearance time; IQR: inter-quartile range; RBM: retrograde bolus movements.

a Children aged ≤18 months (n=24): results from 20 complete pH-MII studies, two studies without pH results and two studies without impedance results are shown.

b Children aged 8 years (n=33): results from 32 complete pH-MII studies and one study without pH results are shown.

Symptoms

Prior to pH-MII monitoring, 12 children/parents spontaneously reported symptoms (16.7% of the infants and 24.2% of the older children) TABLE 4.1. Diaries recorded during the measurement were missing in two children. Twenty-seven children did experience symptoms during pH-MII monitoring, of whom 21 reported non-specific and unlikely to be GER related (e.g. sneezing, hiccup) or very few (<3 times per 24 hours) symptoms. As a result, symptom analysis was performed in only four infants (coughing, belching and twice crying) and two older children (coughing and nausea/burping/regurgitation/vomiting). SI and SAP were positive in 1/6 (16.7%) and 3/6 (50.0%), respectively. If only acidic episodes were considered, SI and SAP were positive in 0/6 and 4/6 (66.7%), respectively. Without manual correction, only three of these latter four children had a positive SAP.

Questionnaire

Twenty-four (72.7%) 8-year old children completed the Manterola questionnaire SUPPLEMENTARY TABLE 4.2. Demographics, RI and number of RBM of these children did not significantly differ from the nine children who did not complete the questionnaire SUPPLEMENTARY TABLE 4.3. The score was suggestive for GERD in seven (29.2%) children. Nocturnal cough (n=7), regurgitation (n=6, weekly in four), dysphagia (n=5) and heartburn (n=5, weekly in one and daily in one) were the most frequently reported symptoms. In only 2/7 children abnormal pH results were found: a RI of 13% in a child with complaints of heartburn at least once a month and an index of 14% in a child with occasional chest pain. pH-MII parameters (automated or manual), SI and SAP did not differ significantly between children with a high (>3) or low (≤3) score.

Change of anti-reflux treatment SUPPLEMENTARY TABLE 4.4

The majority (22/24; 91.7%) of infants were using anti-reflux medication prior to the pH-MII study. In infants, medication was continued in three (one abnormal and two indeterminate pH results), discontinued in 18 (four indeterminate, twelve normal and two unreliable pH results), and discontinued in one infant with abnormal pH results who underwent Nissen fundoplication.

Of the older children, only 2/33 (6%) were using anti-reflux medication prior to the pH-MII study. Medication was discontinued in both (normal pH results). Upper endoscopy was performed in three children with abnormal pH results, in 2/3 PPI was started for mild esophagitis. In two children (one with abnormal pH results and one with night cough) medication was started without endoscopy.

DISCUSSION

In this study we evaluated acid and non-acid GER using pH-MII monitoring in 57 children with EA in infancy and at school-age. Observed RBM were mainly non-acid boluses (infants: 62% of RBM, older children: 64% of RBM) and mixed boluses (infants: 58% of RBM, older children: 75% of RBM).

Compared to available reference values in children without EA (asymptomatic neonates or children with symptoms), we found similar results for RI, number of RBM FIGURE 4.2A and BCT [22-25].

Although several groups have published their pH-MII monitoring results in children with EA, reference values are lacking [2, 11, 12, 26-30]. Differences in patient selection and study protocols makes comparing results difficult. For instance, one study in 35 children with EA continued PPI therapy, while medication was discontinued in other studies [26]. Moreover, they included children of all ages (0.3-17.2 years) while two other studies focused on infants/toddlers [29] and school-aged children [11]. In the latter study children with non-acid reflux were excluded [11]. Compared to studies in children with EA, number of RBM in infants in our study was high compared to a small group of Dutch children, but similar to other cohorts [2, 11, 30]. Results in 8-year old children were comparable. We found a lower RI in both infants (2.6% vs 5.8-6.1%) and older children (0.3% vs 2.5-8.3%) FIGURE 4.2C. RI was similar in 35 Australian children (aged 0-17 years) [26].

In our study, abnormal GER/GERD was diagnosed in 10/57 children (17.5%: RI>7% n=6, positive SI/SAP n=4). This is much lower than the 54% of Danish children with EA and abnormal RI [28]. Others reported 38%-45%, but they used different cut-offs for RI (>4.2% or >5% in children <12 months; >10% in older children) [13, 29]. Tube feeding was an exclusion criteria in the present study, which could have resulted in exclusion of children with GERD. When children with fundoplication surgery were considered as having GERD, a total of 31.6% of abnormal GER/GERD was found.

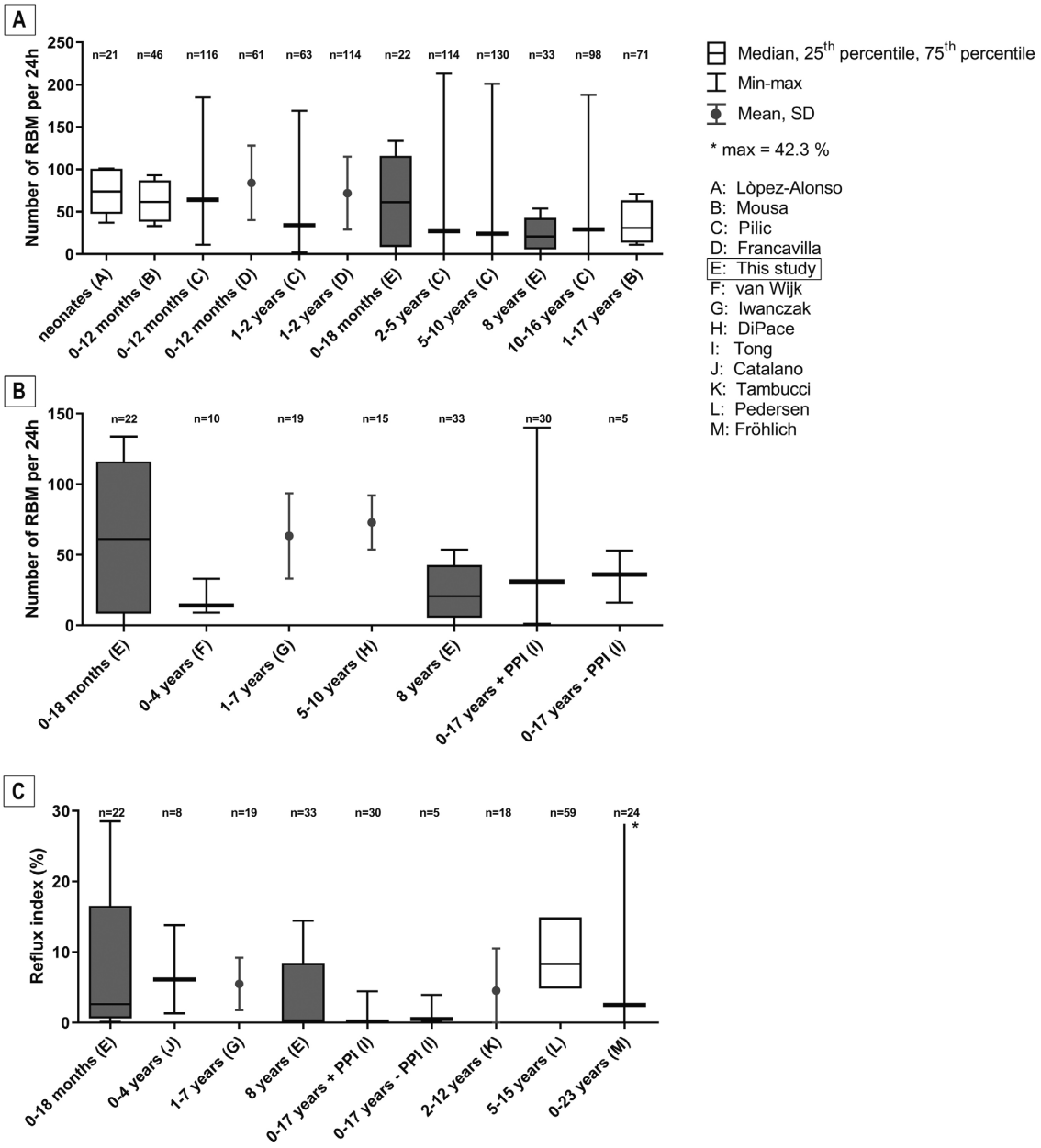

Figure 4.2 pH-MII parameters (number of retrograde bolus movements (RBM) and reflux index) of study cohort compared to available reference values in A) children without esophageal atresia (asymptomatic neonates or children with gastrointestinal, pulmonary or neurological symptoms) and B) and C) children with esophageal atresia.

Symptom recording was insufficient for symptom association analysis as in 10/12 symptomatic children (spontaneously reported prior to pH-MII monitoring) symptoms were absent during pH-MII monitoring. A previous study in 20 children found a recording failure in 52% of coughs and a time lag of 11 seconds between the cough and the recording in the log [31].

The Manterola questionnaire [18] was suggestive for GERD in 29% of 8-year old children, but in only 2/7 a RI>7% was found. Compared to symptomatic 130 children without EA (aged 5-10 years) they had similar number of RBM (21 vs 24), but a lower mean BCT (11 vs 17 second) [22]. We found similar pH-MII parameters in children with low and high Manterola scores, possibly due to a larger day-to-day variability of pH-MII studies in EA patients, or perhaps disturbed impedance patterns make pH-MII studies unsuitable for GER detection in EA patients [32]. Dysphagia was scored positive by 5/7 children with a positive Manterola questionnaire, which may be the result of dysmotility, eosinophilic esophagitis or strictures rather than GER. Furthermore, regurgitation was also scored often (6/7) which – in children with EA – can also be regurgitation from the esophagus rather than the stomach. It may therefore be that the Manterola questionnaire is not suitable for EA patients.

After visual validation of RBM identified as such by the software, 39% was deleted from the tracings. These were mainly non-acid swallows, which the software incorrectly identified as RBM SUPPLEMENTARY FIGURE 4.1 . Abnormal esophageal motility, stasis of fluids and gas caused disturbed patterns which were misinterpreted by the software. Stasis of fluids was mostly present in Z3-Z4, at the level of the esophageal anastomosis. The software did not recognize this stasis and measured a shorter BCT. This is in accordance with previous literature [33]. In automated analysis, swallows following RBM were sometimes misclassified as proximal GER events. Air in the esophagus after a swallow showed a pattern that was recognized as GER by the software.

Previous studies show high inter- and intra-observer variability in pH-MII analysis [34, 35]. The high percentage of deleted RBM raises the question how accurate pH-MII analysis in EA patients is. We believe this number is too high to ignore and to perform automated analyses without manual revision. Manual revision, however, carries the risk of greater inter-observer variability. Refinement of automated software is needed to identify impedance reflux patterns in patients with complex motility disorders such as EA.

The recent ESPGHAN-NASPGHAN Guideline recommends to treat all EA patients with anti-acid treatment in the first year of life and to monitor GER with pH-MII monitoring and/or endoscopy at time of discontinuation (regardless of symptoms) and during long-term follow-up in symptomatic children [6]. However, no studies have been performed to show benefit of routine pH-MII monitoring in EA patients and a recent SR showed evidence – albeit of low quality – that prophylactic anti-reflux medication does not prevent stricture formation

after EA repair [36]. As discussed above reflux in our patients was mainly non-acid. In infants, symptoms were mainly associated with non-acid RBM, while symptoms in older children were mainly associated with acid RBM [29]. Treatment options of non-acid GER are limited. A small double-blinded placebo controlled RCT in children showed that Baclofen inhibits transient lower esophageal sphincter relaxation and accelerates gastric emptying, but is dissuaded in guidelines as a first-choice therapy in children because of known side effects in adults [4, 37]. Surgical anti-reflux procedures are available, but have side effects and it is unclear which patients would benefit. Further research is needed to determine the optimal duration of anti-acid therapy after EA repair.

The strengths of our study are the manual evaluation of RBM, the inclusion of both symptomatic as well as asymptomatic children with EA, and both infants and older children. International guidelines recommend to monitor GER at time of discontinuation of anti-acid treatment (around one year) and during long-term follow-up in symptomatic children with EA [6]. Our study is the first to show pH-MII results in these two age-groups. Still, some limitations need to be mentioned. First, two different pH electrodes were used. Although significant differences have been found in acid exposure times between ISFET, glass and antimony electrodes, our results from both catheters were similar [38]. Second, only 52% of eligible children of our follow-up program were included. Since demographics did not differ and the majority (79%) was asymptomatic, selection bias does not seem to be a major factor influencing our results. Third, only RBM recognized by the software were manually reviewed and modified. This method might have resulted in underreporting of reflux events. Although the software is designed to over-detect reflux events, we cannot exclude the option that episodes were missed. Last, due to the lack of longitudinal data we did not compare results between infants and older children. Infants seem to have worse pH-MII parameters compared to older children, however differences in type of feeding (liquid vs solid food), body position during feeding, and other demographics (i.e. thoracoscopic surgery, use of anti-reflux medication and history of fundoplication surgery) would have made the comparison unreliable.

In conclusion, most infants and school-aged children with EA off medication have a normal RI, yet experience a significant number of non-acid RBM. After manual revision of the tracings a high percentage of RBM was deleted. These were mainly non-acid swallows which the software incorrectly identified as RBM. Our data show that automated impedance analysis software needs refinement for use in infants and children with EA and question the need for standard anti-acid therapy in these patients.

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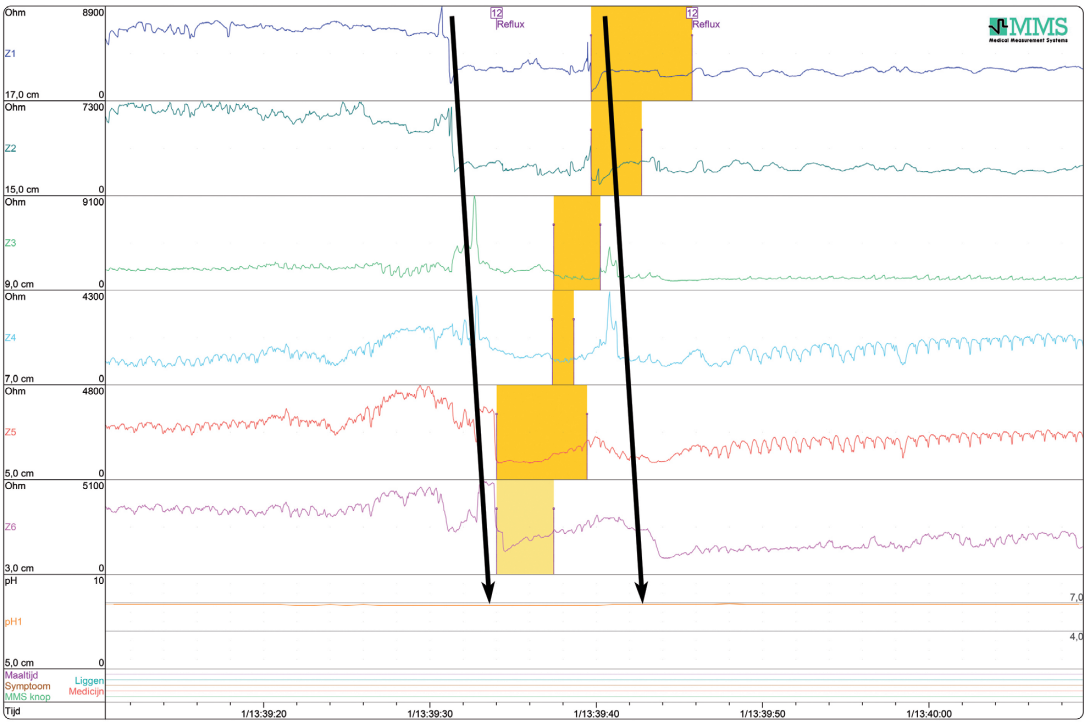

Supplementary figure 4.1 Screenshot: automated analysis of MMS database software misinterprets two swallows (arrows) as being a non-acid retrograde bolus movement.

Supplementary table 4.1 Patient demographics of included children (n=57) and children without pH-MII study (n=52)

	Children included (N=57)	**Children not included (N=52)**	
	n (%) / median (min; max; IQR)	**n (%) / median (min; max; IQR)**	**p-value**
Male gender	29 (50.9)	34 (65.4)	0.126
Gestational age (weeks)	38.3 (28.9; 42.3; 36.8-40.1)	37.7 (32.0; 41.3; 35.9-39.9)	0.163
Prematurity	14 (24.6)	21 (40.4)	0.077
Birthweight (gram)	2685 (854; 3810; 2150-3125)	2750 (1180; 3995; 1909-3270)	0.785
Small for gestational age	8 (14.0)	8 (15.4)	0.842
Type of esophageal atresia			
– Gross type A	1 (1.8)	5 (9.6)	0.101 [a]
– Gross type C	55 (96.5)	47 (90.4)	
– Gross type D	1 (1.8)	0	
Type of esophageal correction			
– Primary anastomosis	53 (93.0)	47 (90.4)	0.734
– Delayed anastomosis	4 (7.0)	5 (9.6)	
Type of surgery			
– Thoracoscopy	25 (43.9)	26 (50.0)	0.459 [b]
– Thoracotomy	31 (54.4)	22 (42.3)	
– Converted	1 (1.8)	2 (3.8)	
– Unknown	0	1 (1.9)	

Non-parametric Mann-Whitney U test for continues variables and Pearson's chi-square test or Fisher's exact test for categorical variables.

a Esophageal atresia Gross type A versus other types (Gross type C + D).

b Thoracoscopy versus thoracotomy (including conversion).

Supplementary table 4.2 Gastrointestinal questionnaire 8-year old children (24/33=72.7%)

Questions to detect gastroesophageal reflux	Answer	Manterola score	n (%)
Do you have complaints of burning reflux (burning sensation behind your breastbone)?	Never	0	16 (66.7)
	At least once a month	1	5 (20.8)
	At least once a week	2	2 (8.3)
	Daily	3	1 (4.2)
Do you have complaints of regurgitation of stomach contents?	Never	0	14 (58.3)
	At least once a month	1	6 (25.0)
	At least once a week	2	4 (16.7)
	Daily	3	0
Do you have problems with swallowing?	No	0	18 (75.0)
	Yes	1	6 (25.0)
Do you have complaints of pain on the chest?	Never	0	17 (70.8)
	Occasional	1	7 (29.2)
	Daily	2	0
Do you have nightly coughs?	Never	0	8 (33.3)
	Occasional	1	16 (66.7)
	Each night	2	0
Do you have complaints of hoarseness?	No	0	22 (91.7)
	Yes	1	2 (8.3)
Do you have asthma?	No	0	24 (100)
	Yes	1	0
Other questions asked	**Answer**		**n (%)**
Are you able to eat everything?	No		5 (20.8) [a]
	Yes		19 (79.2)
Are you able to eat as much as your peers?	No		7 (29.2)
	Yes		17 (70.8)
Are you able to eat as fast as others?	No		13 (54.2)
	Yes		11 (45.8)
Is it necessary to drink while you eat?	No		13 (54.2)
	Yes		11 (45.8) [b]
Do you ever feel nauseous after eating?	No		17 (70.8)
	Yes		7 (29.2) [c]
Are you easily feeling full after eating?	No		15 (62.5)
	Yes		9 (37.5) [d]
Do you ever feel bloated after eating?	No		15 (62.5)
	Yes		9 (37.5) [e]

Manterola score: Manterola et al. Initial validation of a questionnaire for detecting gastroesophageal reflux disease in epidemiological settings. J Clin Epidemiol. 2002;55(10):1041-5.

a Cooked eggs (n=1); hot dogs (n=1); garden peas, beans, cheese and potatoes (n=1); soft drinks (n=1); candy, bananas, apples and hot dogs (n=1).

b The Manterola Questionnaire reported dysphagia in two children, chest pain in three children (one also complained of dysphagia), and regurgitation in two children. In the other five children none of these symptoms were reported.

c A few times a week (n=3); a few times a month (n=2); a few times a year or less (n=2).

d Daily (n=1); a few times a week (n=4); a few times a month (n=1); a few times a year or less (n=3). Two children had a history of Nissen fundoplication.

e Daily (n=1); a few times a week (n=1); a few times a month (n=3); a few times a year or less (n=4).

Supplementary table 4.3 Patient demographics of 8-year old children who were asked to fill in the gastrointestinal questionnaire (N=33)

	Questionnaire completed (N=24)	**No questionnaire (N=9)**	
	n (%) / median (min; max; IQR)	**n (%) / median (min; max; IQR)**	**p-value**
Male gender	9 (37.5)	6 (66.7)	0.239
Gestational age (weeks)	39.0 (28.9; 42.3; 37.3-40.7)	37.7 (34.6; 40.1; 36.0-38.7)	
Prematurity	4 (16.7)	3 (33.3)	0.358
Birthweight (gram)	3030 (1080; 3810; 2238-3368)	2615 (1905; 3180; 2143-2925)	
Small for gestational age	3 (12.5)	1 (11.1)	1.000
Type of esophageal atresia			
– Gross type A	1 (4.2)	0	1.000 [a]
– Gross type C	22 (91.7)	9 (100)	
– Gross type D	1 (4.2)	0	
Type of esophageal correction			
– Primary anastomosis	23 (95.8)	7 (77.8)	0.174
– Delayed anastomosis	1 (4.2)	2 (22.2)	
Type of surgery			
– Thoracoscopy	6 (25.0)	2 (22.2)	1.000 [b]
– Thoracotomy	18 (75.0)	7 (77.8)	
Reflux index (%)	0.3 (0; 11.8; 0.1-1.9)	0.3 (0; 14.4; 0.1-2.7)	0.651
Number of RBM	20.7 (5.8; 48.9; 12.7-27.1)	20.9 (0; 53.7; 10.1-35.4)	0.953

Non-parametric Mann-Whitney U test for continues variables and Pearson's chi-square test or Fisher's exact test for categorical variables.

a Esophageal atresia Gross type A versus other types (Gross type C + D).

b Thoracoscopy versus thoracotomy (including conversion).

Supplementary table 4.4 Change of anti-reflux treatment after pH-MII study

Age ≤ 18 months (N=24)	**abnormal pH results n=2**	**indeterminate pH results n=6**	**normal pH results n=14**	**unknown pH results n=2**
Continuation without anti-reflux medication	0	0	2	0
Discontinuation of anti-reflux medication	0	4	12	2
Continuation of anti-reflux medication	1	2	0	0
Fundoplication surgery + discontinuation of anti-reflux medication	1	0	0	0
Age 8 years (N=33)	**abnormal pH results n=4**	**indeterminate pH results n=2**	**normal pH results n=26** [a]	**unknown pH results n=1** [b]
Continuation without anti-reflux medication	0	2	23	1
Discontinuation of anti-reflux medication	0	0	2	0
Start anti-reflux medication	1	0	1 [c]	0
Upper endoscopy ± start anti-reflux medication	3 [d]	0	0	0

a Nissen fundoplication surgery was performed prior to the pH-MII study in 7/26 children with normal pH results.

b Nissen fundoplication surgery performed prior to the pH-MII study.

c In one child with normal pH-MII results, anti-reflux medication was started to treat night cough.

d Upper endoscopy revealed normal esophagus in one child (no further actions) and mild esophagitis in two children for which treatment with proton pump inhibitors was started.

5

Risk factors for refractory anastomotic strictures after oesophageal atresia repair: a multicentre study

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Floor W.T. Vergouwe, John Vlot, Hanneke IJsselstijn, Manon C.W. Spaander, Joost van Rosmalen, Matthijs W.N. Oomen, Jan B.F. Hulscher, Marc Dirix, Marco J. Bruno, Maarten Schurink, René M.H. Wijnen, on behalf of the DCEA study group.

See the Appendix for a list of the DCEA study group members of the participating centres.

ABSTRACT

Objective

To determine the incidence of refractory anastomotic strictures after oesophageal atresia (OA) repair and to identify risk factors associated with refractory strictures.

Methods

Retrospective national multicentre study in patients with OA born between 1999 and 2013. Exclusion criteria were isolated fistula, inability to obtain oesophageal continuity, death prior to discharge, and follow-up <6 months. A refractory oesophageal stricture was defined as an anastomotic stricture requiring ≥5 dilations at maximally 4-week intervals. Risk factors for development of refractory anastomotic strictures after OA repair were identified with multivariable logistic regression analysis.

Results

We included 454 children (61% male, 7% isolated OA (Gross type A)). End-to-end anastomosis was performed in 436 (96%) children. Anastomotic leakage occurred in 13%. Fifty-eight per cent of children with an end-to-end anastomosis developed an anastomotic stricture, requiring a median of 3 (range 1-34) dilations. Refractory strictures were found in 32/436 (7%) children and required a median of 10 (range 5-34) dilations. Isolated OA (OR 5.7; p=0.012), anastomotic leakage (OR 5.0; p=0.001) and the need for oesophageal dilation ≤28 days after anastomosis (OR 15.9; p<0.001) were risk factors for development of a refractory stricture.

Conclusions

The incidence of refractory strictures of the end-to-end anastomosis in children treated for OA was 7%. Risk factors were isolated OA, anastomotic leakage and the need for oesophageal dilation less than 1 month after OA repair.

INTRODUCTION

Oesophageal atresia (OA) with or without a tracheo-oesophageal fistula (TOF) is a rare anatomical anomaly (2.43:10,000 births) [1]. Dedicated centres have reported survival rates up to 95% [2, 3]. However, anastomotic stricture formation is still the most frequent postoperative complication (17%-59%), occurring mostly in the first year of life [4, 5].

Data on oesophageal stricture formation after OA repair and potential risk factors is scarce [6-12]. A recent single-centre retrospective study found postoperative oesophageal strictures (≥4 dilations, no interval specified) in 21.5% of OA patients (26/121), thoracoscopic and staged OA repair were both associated with stricture formation [6].

A uniform definition of an oesophageal stricture after OA repair is lacking, which makes comparing different studies difficult. Most studies define an oesophageal stricture as any narrowing of oesophageal lumen requiring at least one dilation [5, 7, 9]. However, in current literature definitions vary based on frequency of dilations [6, 13-17], luminal diameter [12], or symptomatology [8, 10]. In some centres patients with OA are routinely subjected to a series of three dilations, even when symptoms and luminal narrowing have disappeared.

Refractory strictures require frequent dilations and therefore result in a high burden for both child and parents, including frequent anaesthesia, hospital stay and risk of perforation. The newest European Society of Gastrointestinal Endoscopy-European Society for Paediatric Gastroenterology Hepatology and Nutrition Guideline on Pediatric Endoscopy suggests the following definition of a benign refractory oesophageal stricture in children: an anatomic restriction without endoscopic inflammation that results in dysphagia after a minimum of five dilations at maximally 4-week intervals [18].

We hypothesised that anastomotic leakage and thoracoscopic OA repair will increase refractory oesophageal stricture formation. In a large multicentre cohort of children born with OA in the Netherlands, we retrospectively determined the incidence of postoperative dilations and refractory anastomotic strictures. We studied possible determinants of refractory stricture formation with focus on strictures of end-to-end anastomoses.

METHODS

Patients

We included all OA patients born between 1999 and 2013 who were treated for OA in one of the participating centres. Data until June 2016 were included, ensuring minimum follow-up of 2.5 years. Exclusion criteria were: isolated TOF (Gross type E) [19], inability to obtain oesophageal continuity, death prior to discharge, and follow-up less than 6 months.

Five of the six university hospitals involved in neonatal surgery – all members of the Dutch Consortium of Esophageal Atresia (DCEA) Study Group – participated (see SUPPLEMENTARY APPENDIX). The Medical Ethics Committee of Erasmus MC concluded that the Dutch Medical Research Involving Human Subjects Act did not apply to the study protocol (protocol ID MEC-2016-570). Ethics approval from the local committees in the other participating centres was obtained.

Data collection

Baseline demographics and outcome data at follow-up were retrieved from patient records. Major associated anomalies included Ravitch' paediatric surgical index diagnoses [20], major cardiac anomalies (cardiac malformations requiring surgical correction or cardiological follow-up), other congenital malformations requiring major surgical interventions, and malformations seriously affecting normal function (e.g. tethered cord with neurogenic bladder function). All other anomalies were considered minor (e.g. small atrial septal defect closing spontaneously). Prematurity was defined as gestational age <37 weeks. VACTERL (vertebral defects, anal atresia, TOF with OA, cardiac anomalies, renal anomalies and limb anomalies) association was defined according to Solomon [21]. Type of OA was classified according to Gross [19]. A child was considered to have gastro-oesophageal reflux disease (GORD) if pH monitoring showed pathological reflux, if upper endoscopy showed oesophagitis or if antireflux surgery was performed. Furthermore, frequent aspiration, typical symptoms with spontaneous reflux present at contrast oesophagography, or symptom relief using antireflux drugs were considered to indicate GORD. Anastomotic leakage was defined as leakage visible at contrast oesophagography or necessitating placement of a chest tube postoperatively.

Definitions of strictures

A stricture was defined as a symptomatic stenosis of an anastomosis for which dilation was indicated. A stricture requiring dilation ≤28 days after OA repair was considered 'early'. A refractory stricture was defined as an anastomotic (end-to-end, oesophagojejunal or oesophagogastric) stricture requiring ≥5 dilations at maximally 4-week intervals [18].

Data analysis

Data are presented as frequencies or as medians (minimum; maximum; IQR). Pearson's X^2 test, Fisher's exact test and the non-parametric Mann-Whitney U test were used for statistical comparison between children with and without a refractory stricture of the end-to-end anastomosis. Multivariable logistic regression analysis was performed to identify risk factors for refractory strictures of the end-to-end anastomosis. Predefined risk factors for refractory strictures were (based on previous literature): gestational age, isolated OA (Gross type A), thoracoscopic correction, anastomotic leakage and early stricture (≤28 days after anastomosis). Centre was also included as an independent variable in the logistic regression model. The Hosmer-Lemeshow goodness-of-fit test was used to assess whether the model adequately describes the data. Because in several studies a *clinically significant* stricture – to be distinguished from a *refractory* stricture – is defined as a stricture requiring ≥3 dilations, findings from children with and without a stricture requiring ≥3 dilations were also compared including identification of risk factors. Data were analyzed with SPSS V.21.0 (SPSS).

RESULTS

We included 454/563 (80.6%) children treated in one of the participating centres. Reasons for exclusion were: isolated TOF (n=31), no oesophageal continuity obtained (n=2), early death (n=59), follow-up <6 months (n=15), and missing data (n=2). Six (1.3%) children who died after discharge and after the age of 6 months (median of 576 (range 207-1729) days) were included.

Demographics

Thoracotomy with primary anastomosis was performed most frequently (357/454; 78.6%) TABLE 5.1. Oesophageal continuity was obtained with a jejunal interposition or gastric pull-up in 18/454 (4.0%) children. Stricture formation was the reason for oesophageal replacement at an older age in three children with isolated OA.

Anastomotic strictures

An anastomotic stricture was documented for 262/454 (57.7%) children: 251/436 (57.6%) children with an end-to-end anastomosis (median (minimum; maximum; IQR) of 3 (1; 34; 1-5) dilations); 9/13 (69.2%) children with a jejunal interposition (median of 5 (3; 32; 4-16) dilations); and 2/5 (40.0%) children with a gastric pull-up (two and five dilations) TABLE 5.2. FIGURE 5.1 illustrates the number of dilations performed in children with an end-to-end anastomosis.

Table 5.1 Patient demographics (N=454)

		n (%) median (min; max; IQR)
Male gender		277 (61.0)
Age at last follow-up (years)		6.6 (0.6; 16.9; 3.7-10.9)
Gestational age (weeks)		38.0 (25.6; 42.9; 35.9-40.0)
Prematurity		161 (35.5)
Birthweight (gram)		2780 (725; 4505; 2115-3200)
Type of oesophageal atresia	Gross type A (isolated OA)	30 (6.6)
	Gross type B (OA with proximal TOF)	3 (0.7)
	Gross type C (OA with distal TOF)	409 (90.1)
	Gross type D (OA with dual TOFs)	12 (2.6)
	Gross type E (isolated TOF)	0
Associated problems	Major associated anomaly	140 (30.8)
	Major cardiac anomaly	39 (8.6)
	VACTERL association	71 (15.6)
	Syndromic diagnosis [a]	33 (7.3)
Type of oesophageal correction [b]	Primary anastomosis	405 (89.2)
	Primary anastomosis with Livaditis lengthening	2 (0.4)
	Delayed anastomosis	28 (6.2)
	Delayed anastomosis with Livaditis lengthening	1 (0.2)
	Oesophageal replacement	18 (4.0)
Type of surgery	Thoracoscopy	52 (11.5)
	Thoracotomy	397 (87.4)
	Converted	5 (1.1)
Chest tube postoperatively		143 (31.5)
Anastomotic leakage [c]		60 (13.2)
Recurrent tracheo-oesophageal fistula [d]		19 (4.2)
Initial days on ventilator		2 (0; 89; 1-4)
Need for gastrostomy [e]		95 (20.9)
Antireflux medical therapy after oesophageal atresia repair [f]	Yes	399 (87.9)
	Unknown	9 (2.0)
History of gastro-oesophageal reflux [g]		223 (49.1)
Antireflux surgery [h]		81 (17.8)

IQR: inter-quartile range; max: maximum; min: minimum; OA: oesophageal atresia; TOF: tracheo-oesophageal fistula.

a Down syndrome (n=13), Goldenhar syndrome (n=8), CHARGE syndrome (n=5), Megarbane syndrome (n=1), Silver-Russell syndrome (n=1). Treacher Collins syndrome (n=1), 22q11.2 deletion syndrome (n=1), caudal duplication syndrome (n=1), 22q11.2 microduplication syndrome (n=1) and Trisomy 18 (n=1).

b Oesophageal continuity obtained at a median of 2 (range 0-2539) days after birth. Oesophageal replacement: jejunal interposition (n=13) and gastric pull-up (n=5).

c At a median of 6 (range 0-63) days after oesophageal continuity was obtained.

d At a median of 107 (range 12-5032) days after initial surgery (primary anastomosis or gastrostomy in staged repair). In two children with long gap OA a TOF arose after laryngotracheal reconstruction for a subglottic stenosis (fistula at day 3698) and after recurrent anastomotic leakage (fistula at days 203 and 3498).

e At a median of 6 (range 0-3098) days after birth. Reasons: staged repair (n=42), feeding difficulties (n=22), oesophageal strictures (n=9), anastomotic leakage (n=7), gastro-oesophageal reflux disease (n=7), decompression tension on stomach during ventilation (n=4), prematurity (n=2), access to stomach to retrieve broken bougie tip (n=1), and unknown (n=1).

f H2 antagonist ± prokinetic drug (n=319), proton pump inhibitor ± prokinetic drug (n=47) or prokinetic drug monotherapy (n=33). Duration of medical therapy: <3 months (n=51), 3-6 months (n=79), 6-12 months (n=82), >12 months (n=150), unknown (n=37).

g Diagnosis of gastro-oesophageal reflux disease: antireflux surgery performed (n=76), pathological pH-monitoring (n=61), pathologic contrast oesophagography with typical symptoms (n=31), oesophagitis (n=21), typical symptoms with good response to medical therapy (n=18), and frequent symptoms of aspiration (n=16).

h Nissen (n=56), Thal (n=7), Toupet (n=2), Boix-Ochoa fundoplication (n=1) and Boerema anterior gastropexy (n=15), performed at a median of 207 (range 42-2785) days after birth. Redo antireflux surgery was needed in 15 children, with a median time interval after initial antireflux surgery of 399 (range 72-2758) days. One child needed a third surgery (interval of 3317 days) and one child needed a second and third surgery (intervals of 400 and 2640 days).

Table 5.2 Dilation procedures of anastomotic strictures (N=1077) in 262 (57.7%) children

		n (%) **median (min; max; IQR)**
Stricture location	End-to-end oesophageal anastomosis	973 (90.3)
	Oesophagojejunal anastomosis proximal [a]	93 (8.6)
	Oesophagogastric anastomosis gastric pull-up	11 (1.0)
Diameter of dilation procedure (mm)		9 (3; 20; 7-10)
Type of dilation procedure	Bougie	733 (68.1)
	Balloon (endoscopic)	138 (12.8)
	Balloon (fluoroscopic)	170 (15.8)
	Unknown	36 (3.3)
First type of dilation	Bougie	201 (76.7)
	Balloon	50 (19.1)
	Unknown	11 (4.2)
Perforation after bougie/balloon dilation procedure	Bougie	9 (1.2)
	Balloon	5 (1.6)
Tight stricture	Yes	95 (8.8)
	No	664 (61.7)
	Unknown	318 (29.5)
Ability to pass an endoscope through the stricture	No passage possible	313 (29.1)
	Passage possible	101 (9.4)
	Stricture visible, but passage unknown	220 (20.4)
	No relevant stricture visible [b]	96 (8.9)
	Unknown	347 (32.2)

a Stricture of proximal anastomosis (n=45), distal anastomosis (n=40) or both proximal and distal anastomosis (n=8).

b No resistance during the dilation procedure and no mucosal tears after the dilation procedure.

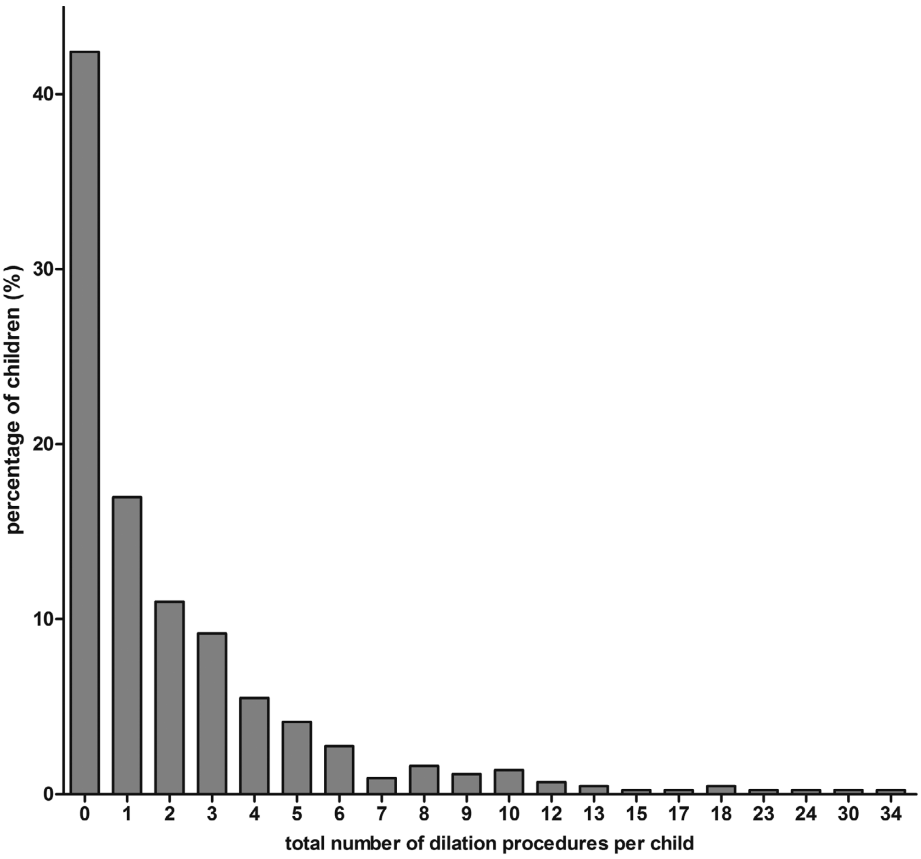

Figure 5.1 Anastomotic dilation procedures performed in children with oesophageal end-to-end anastomosis (N=436).

Refractory strictures developed in 32/436 (7.3%) children with an end-to-end anastomosis (varying between centres: 1.6%-13.3%, see SUPPLEMENTARY FIGURE 5.1 . A median of 10 (5; 34; 8-15) dilations were performed; the fifth dilation at a median of 110 (49; 158; 81-124) days after anastomosis. Refractory strictures of the oesophagojejunal anastomosis developed in 2/13 (15.4%) jejunal interpositions: one stricture of a proximal anastomosis requiring 32 dilations (fifth dilation at day 86 after anastomosis) and one stricture of a distal anastomosis requiring 15 dilations (fifth dilation at day 72 after anastomosis).
Eighteen of 81 (22.2%) children who underwent fundoplication surgery had developed a refractory stricture prior to antireflux surgery. After antireflux surgery 31 (39.3%) children still needed oesophageal dilation, with a median of 3 (1; 29; 1-7) dilations per child. Two (2.5%) children developed a refractory stricture after antireflux surgery (Nissen fundoplication and Boerema anterior gastropexy with hiatoplasty, respectively).

SUPPLEMENTARY TABLE 5.1 summarises details on other treatments of strictures (i.e. stent placement, mitomycin application and stricture resection).

Determinants of refractory anastomotic strictures

TABLE 5.3 summarises characteristics of children with and without a refractory stricture of the end-to-end anastomosis. Results from multivariable logistic regression analysis (adjusted for centre) in children with an end-to-end anastomosis demonstrated that isolated OA (OR 5.7; p=0.012), anastomotic leakage (OR 5.0; p=0.001) and an early stricture (OR 15.9; p<0.001) were associated with refractory stricture formation TABLE 5.4 . Thoracoscopic OA repair was not significantly associated with refractory strictures. In multivariable logistic regression analysis 6/436 children were excluded (missing values for gestational age).

SUPPLEMENTARY TABLE 5.2, 5.3 AND 5.4 summarise results from multivariable logistic regression analysis for strictures requiring ≥3 dilations (definition of a clinically significant stricture in several studies).

Table 5.3 Strictures of oesophageal end-to-end anastomosis (N=436): characteristics of children with and without a refractory anastomotic stricture (≥5 dilations)

	Refractory stricture [b] **(N=32)**	**No refractory stricture (N=404)**	
	n (%) median (min; max; IQR)	**n (%) median (min; max; IQR)**	**p-value**
Male gender	21 (65.6)	248 (61.4)	0.635
Gestational age (weeks)	37.6 (25.6; 42.0; 35.6-38.9)	38.1 (25.6; 42.9; 36.0-40.0)	0.170
Prematurity	13 (40.6)	136 (33.7)	0.460
Birthweight (gram)	2650 (725; 3440; 2000-2933)	2795 (735; 4505; 2150-3220)	0.152
Isolated OA (Gross type A)	4 (12.5)	11 (2.7)	**0.018**
Major associated anomaly	12 (37.5)	121 (30.0)	0.377
Major cardiac anomaly	2 (6.3)	36 (8.9)	1.000
Syndromic diagnosis	3 (9.4)	26 (6.4)	0.461
Thoracoscopy [a]	5 (15.6)	47 (11.6)	0.567
Staged repair	9 (28.1)	21 (5.2)	**<0.001**
Chest tube	13 (40.6)	116 (28.7)	0.192
Anastomotic leakage	9 (28.1)	49 (12.1)	**0.025**
Recurrent tracheo-oesophageal fistula	2 (6.3)	14 (3.5)	0.331
History of gastro-oesophageal reflux	23 (71.9)	182 (45.0)	**0.001**
Antireflux surgery	2 (6.3)	60 (14.9)	0.289
First dilation with a bougie	27 (84.4)	168 (41.6)	0.593
Early stricture (≤28 days after anastomosis)	12 (37.5)	21 (5.2)	**<0.001**

OA: oesophageal atresia. Bold typeface represent statistically significant p values (p<0.05). Non-parametric Mann-Whitney U test for continuous variables and Pearson's X^2 test or Fisher's exact test (if expected counts were <5) for categorical variables.

a Thoracoscopy was performed in centre A and E: refractory strictures developed in 4/48 (8.3%) and 1/4 (25.0%) thoracoscopic repairs, respectively.

b Antireflux surgery was performed in 18 of 32 (56.3%) children with a refractory stricture: two prior to and 16 after development of a refractory stricture.

Table 5.4 Multivariable logistic regression analysis for refractory anastomotic stricture (≥5 dilations) in children with oesophageal end-to-end anastomosis (N=436)

	OR	**95% CI**	**p-value**
Gestational age (weeks)	0.98	0.85-1.12	0.711
Isolated OA (Gross type A)	5.71	1.48-22.13	**0.012**
Thoracoscopy	0.45	0.14-1.50	0.191
Anastomotic leakage	5.03	1.88-13.43	**0.001**
Early stricture (≤28 days after anastomosis)	15.90	5.89-42.92	**<0.001**

CI: confidence interval; OA: oesophageal atresia; OR: odds ratio. Bold typeface represents statistically significant p values (p<0.05). Adjusted for centre. Hosmer-Lemeshow goodness of fit test p=0.552. Due to missing values for gestational age 6/436 children were excluded from the multivariable logistic regression analysis.

DISCUSSION

In this multicentre national cohort of 454 children born with OA the incidence of anastomotic strictures after end-to-end anastomosis was 57.6%. Refractory stricture of an end-to-end anastomosis requiring ≥5 dilations developed in 7.3% of cases. Isolated OA, anastomotic leakage and early stricture (≤28 days after anastomosis) were associated with refractory stricture development.

The incidence of anastomotic strictures after OA repair in our study (57.7%) is concordant with previous literature (9%-79%) [22]. This wide range reflects the lack of a uniform definition of refractory strictures. Many clinicians decide to surgically intervene after three consecutive dilations. Thus, in several studies a clinically significant stricture is defined as a stricture requiring ≥3 or ≥4 dilations [6, 16, 17]. We recommend to use a uniform definition for refractory anastomotic strictures in future studies: an anastomotic stricture requiring ≥5 dilations at maximally 4-week intervals. This definition distinguishes *refractory* strictures from so called *recurrent strictures*.

Nice et al. found that both thoracoscopic and staged OA repair were associated with stricture formation [6]. These authors considered strictures refractory and clinically significant after ≥4 dilations. Unfortunately, information on the interval between dilations and the duration of follow-up was not provided, which impedes comparison to our study.

Despite better visualization and usually a more limited dissection during thoracoscopic OA repair, opening of the upper pouch can be less than in open surgery which might lead to increased stricture formation. We could however not confirm our hypothesis that thoracoscopic OA repair is associated with refractory stricture formation. The relatively low number of thoracoscopic corrections (n=54 performed in two centres only) may explain this. Two recent literature reviews concluded that the incidence of strictures after both thoracoscopic and open OA repairs is comparable [23-25].

Both in the present and in earlier studies leakage was predictive of anastomotic stricture formation [26, 27]. We assume that leakage enhances inflammation and scarring of the anastomotic area.

Our finding that isolated OA was a risk factor is supported by others [8, 11, 12]. The long gap in isolated OA often requires staged anastomosis or oesophageal replacement. Although correction of a large gap is thought to result in anastomotic tension with subsequent stricture formation, contradictory results have been reported [15, 28]. We included only the uniformly objective variable isolated OA as a potential explanatory variable, since staged repair, long gap OA and oesophageal replacement are correlated to each other.

In children with an isolated OA, the current practice to restore oesophageal continuity is performing a primary anastomosis, either immediately or delayed. In our study only 15/30 children with an isolated OA underwent an oesophageal anastomosis. Children with an isolated OA in whom a primary anastomosis is performed may be at higher risk of developing a refractory stricture than children with other types of OA. Indeed we found that a refractory stricture had developed in 26.7% (4/15). This information can be shared in preoperative parental counseling.

We also found that an early anastomotic stricture predicted the development of a refractory stricture. More severe strictures may occur in the first weeks postoperatively, but early dilation in a still vulnerable anastomosis might be an independent risk factor for refractory strictures. Our data do not allow to draw any conclusions on this subject. Most of the refractory strictures developed within four months postoperatively. We assume that the 'late onset' oesophageal strictures are related to altered food consistency as more solid formulas can cause dysphagia, food impaction, stasis, aspiration or vomiting.

Although others have identified anastomotic tension as a risk factor for strictures, we chose to not include tension as a potential determinant [7-11, 26]. Anastomotic tension is a subjective observation which is usually poorly recorded. Anastomotic leakage is a more objective finding and was found to be a predictor for stricture formation in our study.

Another factor thought to increase stricture development is GORD [5, 11, 26, 27]. Studies are hard to compare as different definitions of GORD are used. Besides, most studies are retrospective without use of standardized protocols to diagnose GORD. Interestingly, prophylactic antireflux drugs did not always reduce stricture formation in OA patients [29-31]. We did not include GORD as a possible determinant in our study as participating centres used different protocols for diagnosis. In our study, antireflux surgery was more frequent in children with a refractory stricture than in those without. It was typically performed after refractory stricture development and should therefore be considered as therapeutic management rather than being a risk factor for stricture formation.

Prematurity, birth weight and cardiac anomalies have been associated with stricture formation, but this was not the case in our study [6, 8, 30].

Several adjuvant treatments are currently available for the treatment of refractory strictures, such as stent placement, intralesional steroid injection, mitomycin C application, endoscopic needle knife incision and resection surgery. Studying the effectiveness of these treatments was outside the scope of our study.

The strengths of our study are the large cohort (covering ~80% of all newborns born with OA in the Netherlands), the long follow-up period and the small number of missing data. Still, some limitations need to be addressed. First, risk factors for refractory strictures after jejunal interposition (2/13) or gastric pull-up (0/5) could not be identified due to the limited sample size. Second, indications for dilations were not recorded reliably in all cases. One of the problems with OA is the associated dysmotility, so some level of stasis is always present. Whether feeding can be ameliorated with dilations is usually decided based on the combination of clinical symptoms and by radiographic findings in selected cases. Third, the method used to open the proximal pouch (monopolar/bipolar electrocautery, knife, scissors) and suture techniques for anastomosis were not recorded. Since anastomotic tension and ischemia are thought to play a role in anastomotic stricture formation, it would be interesting to use innovative new optical techniques to address these aspects in future studies (e.g. deformation sensors in (endoscopic) instruments to quantify tension and spectroscopic assessment of tissue oxygenation and perfusion). Fourth, due to the retrospective design and the absence of uniform protocols for dilations and GORD diagnosis, we were unable to reliably study the relation between these factors and stricture development. Besides, eosinophilic oesophagitis – known to be associated with oesophageal stricture development – could not be included as a risk factor as no standardized upper endoscopies with biopsies were performed in our study cohort [32]. Last, the participating centres differed with regard to the frequencies of thoracoscopic corrections, chest tube placement postoperatively, anastomotic leakage, recurrent TOFs and antireflux procedures. Studying a large cohort with a higher number of thoracoscopic surgeries is needed to examine whether a learning curve is present [32, 33]. Numbers of antireflux procedures performed in different centres might reflect differences in dilation management and GORD protocols between centres.

We observed an alarmingly high number of refractory strictures after end-to-end anastomosis in children with isolated OA (26.7%). Whether these children, those with anastomotic leakage, and those with an early stricture may benefit from supportive care (e.g. adequate acid suppression) aiming to protect the anastomotic area is still unknown.

In conclusion, refractory anastomotic strictures requiring ≥5 dilations had developed in 7.3% of 436 OA patients with an end-to-end anastomosis. A high number (26.7%) was observed after end-to-end anastomosis in children with isolated OA. We observed that isolated OA, anastomotic leakage and early anastomotic stricture (≤28 days after anastomosis) are associated with refractory anastomotic stricture formation. Future prospective multicentre studies should focus on uniform recording of baseline data – including surgical techniques used –, standardized protocols for diagnosis of GORD, eosinophilic oesophagitis [32], and indications and techniques for oesophageal dilations.

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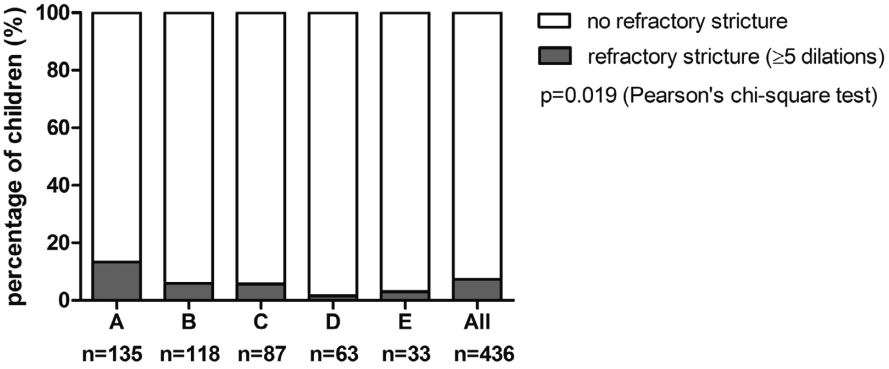

Supplementary figure 5.1 Patient per centre: development of refractory strictures (≥5 dilations) of oesophageal end-to-end anastomosis

Supplementary table 5.1 Stent placement, mitomycin application and stricture resection

Treatment of stricture		**n**
Stent placement [a]	Intraluminal solid silicone stent	25
	Self-expanding silicone stent	7
	Stent of unknown type	12
	Mitomycin application [b]	6
Stricture resection with end-to-end anastomosis [c]		8

a Forty-four stents were placed in seven children (median of 3 (range 1-25) stents. The initial stent was placed after a median of 15 (range 6-26) dilations. In all seven children strictures reoccurred after the first stent placement.

b Mitomycin was applied in two children, in both cases additional dilations were still required.

c Resection surgery was performed in eight different children after median of 14 (range 0-30) dilations, in four children the stricture reoccurred.

Supplementary table 5.2 Strictures of oesophageal end-to-end anastomosis (N=436): characteristics of children with and without an anastomotic stricture requiring ≥3 dilations

	Stricture requiring ≥3 dilations [a] **(N=61)**	**No stricture requiring ≥3 dilations (N=375)**	
	n (%) median (min; max; IQR)	**n (%) median (min; max; IQR)**	**p-value**
Male gender	35 (57.4)	234 (62.4)	0.454
Gestational age (weeks)	37.3 (25.6; 42.0; 35.9-39.0)	38.3 (25.6; 42.9; 35.9-40.0)	**0.036**
Prematurity	26 (42.6)	123 (32.8)	0.158
Birthweight (gram)	2600 (725; 4210; 2000-2965)	2800 (735; 4505; 2154-3251)	**0.016**
Isolated OA (Gross type A)	7 (11.5)	7 (1.9)	**0.002**
Major associated anomaly	18 (29.5)	115 (30.7)	0.845
Major cardiac anomaly	3 (4.9)	35 (9.3)	0.255
Thoracoscopy	12 (19.7)	40 (10.7)	**0.044**
Staged repair	14 (23.0)	16 (4.3)	**<0.001**
Chest tube	18 (29.5)	111 (29.6)	0.988
Anastomotic leakage	14 (23.0)	44 (11.7)	**0.017**
Recurrent tracheo-oesophageal fistula	4 (6.6)	12 (3.2)	0.258
History of gastro-oesophageal reflux	36 (59.0)	163 (43.5)	**0.007**
Antireflux surgery	1 (1.6) [a]	49 (13.1)	**0.009**
Early stricture (≤28 days after anastomosis)	17 (27.9)	16 (4.3)	**<0.001**

OA: oesophageal atresia. Non-parametric Mann-Whitney U test for continuous variables and Pearson's chi-square test or Fisher's exact test (if expected counts were <5) for categorical variables.

a Anti-reflux surgery was performed in 29 of 61 (47.53%) children with a stricture requiring ≥3 dilations: one prior to and 28 after the third dilation of the stricture.

Supplementary table 5. 3 Multivariable logistic regression analysis for anastomotic strictures requiring ≥3 dilations in children with oesophageal end-to-end anastomosis (N=436)

	OR	**95% CI**	**p-value**
Gestational age (weeks)	0.96	0.86-1.06	0.403
Isolated OA (Gross type A)	5.79	1.80-18.57	**0.003**
Thoracoscopy	0.72	0.30-1.72	0.460
Anastomotic leakage	2.93	1.33-6.43	**0.007**
Early stricture (≤28 days after anastomosis)	10.59	4.50-24.90	**<0.001**

CI: confidence interval; OA: oesophageal atresia; OR: odds ratio. Adjusted for centre. Hosmer & Lemeshow goodness of fit test p=0.274. Due to missing values for gestational age 6/436 children were excluded from the multivariable logistic regression analysis.

Supplementary table 5.4 Strictures of oesophagojejunal anastomosis (N=13): characteristics of children with and without an anastomotic stricture requiring ≥3 dilations

	Stricture requiring ≥3 dilations [a] **(N=6)**	**No stricture requiring ≥3 dilations (N=7)**	
	n (%) median (min; max; IQR)	**n (%) median (min; max; IQR)**	**p-value**
Male gender	5 (83.3)	1 (14.3)	**0.029**
Gestational age (weeks)	35.1 (31.4; 37.6; 32.6-37.1)	37.1 (27.9; 38.1; 33.4-38.0)	0.431
Prematurity	4 (66.7)	3 (42.9)	0.592
Birthweight (gram)	2203 (1875; 2729; 2020-2509)	2840 (932; 3230; 1642-2905)	0.668
Isolated OA (Gross type A)	6 (100)	6 (85.7)	1.000
Major associated anomaly	2 (33.3)	3 (42.9)	1.000
Major cardiac anomaly	0	1 (14.3)	1.000
Thoracoscopy	0	0	-
Staged repair	6 (100)	7 (100)	-
Chest tube	4 (66.7)	5 (71.4)	1.000
Anastomotic leakage	1 (16.7)	0	0.462
Recurrent tracheo-oesophageal fistula	0	0	-
History of gastro-oesophageal reflux	2 (33.3)	4 (57.1)	1.000
Antireflux surgery	0	0	-
Early stricture (≤28 days after anastomosis)	1 (16.7)	0	0.462

OA: oesophageal atresia. Non-parametric Mann-Whitney U test for continuous variables and Pearson's chi-square test or Fisher's exact test (if expected counts were <5) for categorical variables.

a Anti-reflux surgery was performed in three of six (50.0%) children with a stricture requiring ≥3 dilations, all three were performed after the third dilation of the stricture.

APPENDIX

DCEA study group members of the centres that participated

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6

High prevalence of Barrett's esophagus and esophageal squamous cell carcinoma after repair of esophageal atresia

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ABSTRACT

Background and aims

Esophageal atresia is rare, but improved surgical and intensive care techniques have increased rates of survival in children, so there are now many adults with this disorder. Many patients with esophageal atresia develop gastroesophageal reflux (GER), raising concerns about increased risk of Barrett's esophagus (BE; prevalence of 1.3%-1.6% in general population) and esophageal carcinoma. We assessed the prevalence of BE and esophageal carcinoma in this population.

Methods

We performed a prospective study of 289 patients with esophageal atresia at the Department of Gastroenterology and Hepatology at Erasmus MC University Medical Center in The Netherlands, from May 2012 through March 2017. One hundred fifty-one (median age, 25.4 years; age range, 16.8–68.6 years) underwent upper endoscopies as part of a surveillance program for (pre)malignant esophageal lesions. Biopsies were collected and analyzed by histology. We collected data on patients' use of medications, tobacco, and alcohol; gastrointestinal symptoms; ability to swallow; complaints of GER; and type of atresia and surgeries. Prevalence of esophageal squamous cell carcinoma (ESCC) was determined using data from the Netherlands Cancer Registry. The number of persons alive on January 1, 2016 in the esophageal atresia cohort and in the general Dutch population were used to calculate the 10-year prevalence of ESCC per 100,000 persons in both populations.

Results

Forty-seven percent of patients with esophageal atresia had a history of GER and 20.5% had undergone fundoplication surgery. Endoscopy revealed normal esophagus in 68.2% of patients, esophagitis in 7.3%, and columnar-lined esophagus in 24.5%. Histology revealed normal mucosa in 50.3% of patients, esophagitis in 23.2%, gastric metaplasia in 17.2%, and BE in 6.6% (at a median age of 31.6 years). A history of fundoplication surgery was associated with BE (P=.03). Three ESCCs developed, in 2 men, at ages of 42, 44, and 60 years. This corresponded to a prevalence of 0.7% in patients with esophageal atresia – a value 108-fold higher than in the same age group in the general population.

Conclusions

The prevalence of BE is 4-fold higher in young adults with esophageal atresia, and the prevalence of ESCC is 108-fold higher, than in the general population. This finding could have important implications for transition of young adults from pediatric care to adult gastroenterology departments to receive life-long endoscopic follow up to facilitate early diagnosis of relevant lesions.

INTRODUCTION

Esophageal atresia (EA) is a rare anatomical anomaly (worldwide prevalence 2.43/10,000 births)[1]. Surgical correction is needed soon after birth. In the last 40 years, improved surgical and intensive care techniques have increased survival rates up to 93% in expert centers and therefore more of these children have reached adulthood [2].

Many EA patients suffer from gastroesophageal reflux (GER) with a reported prevalence of 32.8-54.2% in infancy/childhood and 5.9-66.7% in adolescence/adulthood [3]. Chronic GER may lead to esophageal mucosal injury, resulting in esophagitis, gastric metaplasia (GM) or intestinal metaplasia (IM) also called Barrett's esophagus (BE) [4]. In the general adult population, the prevalence of BE is 1.3%-1.6% and is predominantly diagnosed in middle-aged white males [5-7]. BE is a premalignant lesion and predisposes to esophageal adenocarcinoma (EAC), with an estimated incidence rate of 0.5% per year of follow-up [8].

The high prevalence of GER in EA patients raises concerns about an increased risk of developing BE and EAC in this population [3]. Carcinoma of the upper gastrointestinal tract at a relatively young age has been described in EA patients: eight esophageal carcinoma (three EAC and five esophageal squamous cell carcinoma (ESCC)) [9-13] and two squamous cell carcinoma not related to the native esophagus [14, 15].

Given these findings and the dismal prognosis of patients with symptomatic esophageal cancer, endoscopic surveillance in EA patients was recently recommended in an ESPGHAN-NASPGHAN guideline [16]. We assessed the prevalence of BE and esophageal cancer in a prospective screening and surveillance program in adult EA patients.

MATERIALS AND METHODS

Patients

Since 1999, all EA patients have joined a longitudinal follow-up program at the Pediatric Surgery department of our tertiary referral center [17]. Since April 2013, all adult EA patients (≥17 years) have routinely been referred to the Gastroenterology department for clinical assessment and endoscopic screening and surveillance of (pre)malignant esophageal lesions. We searched our patient registry system and written surgical records for patients born in 1948 to 1999 to identify all EA patients treated in our center and invited these patients for our endoscopic screening and surveillance program.

Ethics

The study protocol was reviewed by the Institutional Review Board of the Erasmus Medical Center (MREC Erasmus MC, protocol ID MEC-2015-093). Formal approval was waived since all handling to the subjects was part of standard clinical care.

Data collection

All data were prospectively collected. Data on medication, tobacco and alcohol use and the occurrence of gastrointestinal symptoms were collected at the outpatient clinic, prior to the endoscopy. Ability to swallow was assessed from dysphagia scores SUPPLEMENTARY TABLE 6.1. Complaints of GER were defined as chest pain, pyrosis or regurgitation. Data retrieved from patient records included type of EA (Gross classification [18]), type of primary surgery, and additional relevant medical history.

GER was considered clinically significant if patients needed fundoplication surgery, if pH-monitoring showed pathological reflux or if – according to the American College of Gastroenterology (ACG) guidelines for GER – upper endoscopy showed typical reflux-induced mucosal lesions [19].

All endoscopic procedures were performed by an experienced gastroenterologist, according to a standardized protocol. The mucosa of the esophagus was examined using white light. In case of suspicion of BE it was switched to Narrow Band Imaging (NBI). From the age of 25 years the esophagus was also stained with Lugol to detect early squamous lesions [20]. Endoscopic landmarks, such as the squamo-columnar junction (Z-line), the proximal margin of gastric folds (GEJ) and the diaphragm, were identified and described. All remarkable findings were noted. Esophagitis and Barrett's epithelium were scored according to the Los Angeles Classification [21] and Prague criteria [22]. Four random biopsies were taken above the GEJ (if end-to-end anastomosis or gastric pull-up had been performed) or above the proximal anastomosis (if a colon, jejunal or ileocecal interposition had been performed). In case of BE four-quadrant biopsies were taken every 2 cm, according to the Seattle protocol [23]. The proposed surveillance intervals for BE are in accordance with the ACG guidelines [4]. In addition, in the absence of BE surveillance intervals of 5 years (age <30 years) or 3 years (age ≥30 years) were advised SUPPLEMENTARY FIGURE 6.1. Endoscopic findings were classified according to the most severe abnormality found at upper endoscopy.

All deceased and non-responding patients were linked to the Netherlands Cancer Registry, managed by the Netherlands Comprehensive Cancer Organisation (IKNL) [24]. Since 1989, the Netherlands Cancer Registry registers all participants diagnosed with cancer in the Netherlands and provides a unique and fully covered database. The 10-years prevalence of

ESCC was determined at January 1 2016 (all patients alive at this date, who were diagnosed with ESCC in the ten preceding years). The number of persons alive at January 1 2016 in the EA cohort and in the general Dutch population were used to calculate the 10-year prevalence of ESCC per 100,000 persons in both populations.

Histology and immunohistochemistry

Biopsy specimens were processed at the Pathology department according to standard procedures: formalin fixed, paraffin embedded, serially sectioned, and stained with hematoxylin & eosin. Biopsies were evaluated by an expert gastrointestinal pathologist for the presence of esophagitis, metaplasia, and dysplastic changes SUPPLEMENTARY TABLE 6.2. Numbers of eosinophils per high-power field were counted. In accordance with the ACG guidelines, we considered the presence of goblet cells obligatory to confirm the diagnosis of BE although malignant transformation in GM has been described [4]. Histological results were classified according to the most severe abnormality at any biopsy.

Statistical analysis

Data are expressed as frequencies or medians (minimum; maximum; inter-quartile range (IQR)). Characteristics of patients with and without BE were compared using Mann-Whitney U tests for continuous variables and Pearson's chi-square or Fisher's exact test (if expected counts <5) for categorical variables. Because confirmation of BE can be limited by sampling error (mosaic pattern of GM and IM [25]) and as BE is thought to evolve from GM, findings from EA patients with and without metaplasia (GM or IM) were also compared.

Univariable logistic regression analysis was used to identify predictors of BE and metaplasia. To reduce bias due to missing values of weight and length (19% missing weight; 15% missing length), multiple imputation was performed for these values in multivariable logistic regression analysis. Multivariable logistic regression analysis of the imputed data was used to identify potential predictors of metaplasia and results were pooled using Rubin's rules. Relevant predictors were selected using likelihood-ratio tests (stepwise backwards; candidate variables: gender, fundoplication surgery, age, (prior) use of alcohol, (prior) smoking and BMI). A p-value less than 0.05 was considered statistically significant. Data were analyzed with SPSS 21.0 (SPSS Inc., Chicago, IL).

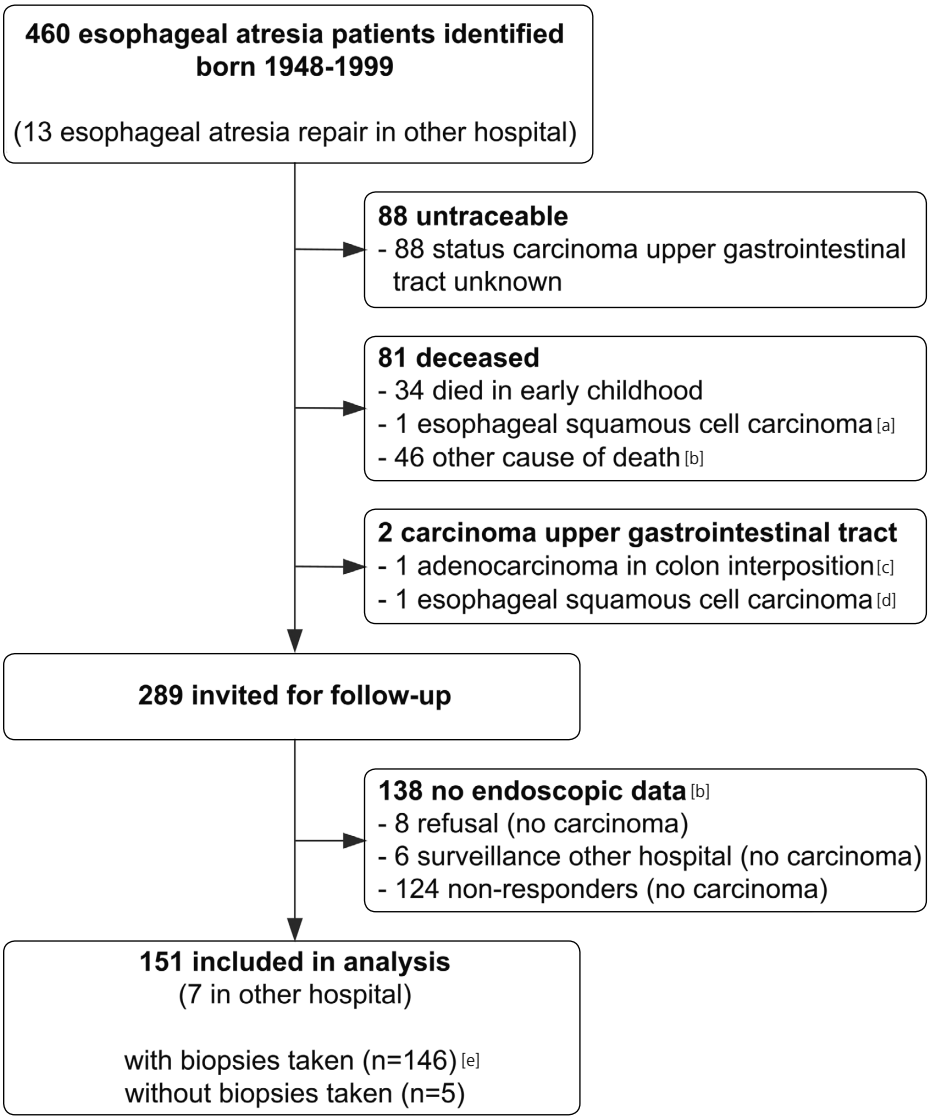

Figure 6.1 Flowchart of esophageal atresia patients.

a Esophageal squamous cell carcinoma (ESCC) in a 45-year old male, second primary ESCC at age 60 years.
b Data (non-traceable match between datasets) provided by the Netherlands Comprehensive Cancer Organisation (IKNL): none of these patients developed esophageal cancer.
c Adenocarcinoma of the thoracic colon interposition in a 48-year old male.
d Mid-esophageal ESCC in a 42-year old male.
e Four patients were already under surveillance for Barrett's esophagus.

Table 6.1 Baseline characteristics of 151 participants of the surveillance program

		n (%)
Male gender		85 (56.3)
Type of esophageal atresia	Type A	16 (10.6)
	Type C	129 (85.4)
	Type D	4 (2.6)
	Type unknown	2 (1.3)
Type of surgery [a]	Primary end-to-end anastomosis	123 (81.5)
	Delayed end-to-end anastomosis	10 (6.6)
	Gastric pull-up or bowel interposition	18 (11.9)
Associated congenital anomalies		77 (51.0)
Genetic diagnosis [b]		7 (4.6)
Diagnosis of gastroesophageal reflux prior to surveillance [c]	Yes	71 (47.0)
	Age in years; median	0.5
	(min; max; IQR)	(0.1; 54.5; 0.2-7.8)
Diagnosis of Barrett's esophagus prior to surveillance [d]	Yes	4 (2.6)
Fundoplication surgery [e]	Yes	31 (20.5)
	Age in years; median	0.5
	(min; max; IQR)	(0.1; 7.5; 0.3-1.8)
Dilation of esophageal stenosis	Yes	88 (58.3)
	Number of dilations; median	5
	(min; max; IQR)	(1; 35; 3-7)
Age at time of first surveillance endoscopy	Age in years; median	25.4
	(min; max; IQR)	(16.8; 68.6; 19.1-36.1)
Body mass index (BMI)	Severe underweight (<16 kg/m^2)	2 (1.3)
	Underweight (16-18.5 kg/m^2)	11 (7.3)
	Normal (18.5-25 kg/m^2)	83 (55.0)
	Mild-moderate overweight (25-30 kg/m^2)	22 (14.6)
	Severe overweight (30-40 kg/m^2)	5 (3.3)
	Missing	28 (18.5)
Anti-reflux medical therapy [f]	Yes, daily use	16 (10.6)
	Yes, when needed	2 (1.3)
	No	124 (82.1)
	Missing	9 (6.0)
Tobacco smoking	Yes	24 (15.9)
	Former smoker (quit>2 years)	9 (6.0)
	No	116 (76.8)
	Missing	2 (1.3)
Alcohol consumption	≤7 units/week	68 (45.0)
	≥8 units/week	10 (6.6)
	Yes, but amount unknown	18 (11.9)
	No alcohol	53 (35.1)
	Missing	2 (1.3)
Dysphagia	Grade I	75 (49.7)
	Grade II	1 (0.7)
	Gastrostomy, no oral diet	1 (0.7)
	No dysphagia	70 (46.4)
	Missing	4 (2.6)
Gastroesophageal reflux complaints	Yes	47 (31.1)
	No	96 (63.6)
	Missing	8 (5.3)

a End-to-end anastomosis with Livaditis myotomy (n=9). Gastric pull-up (n=1), colon (n=15), jejunal (n=1) and ileocecal interposition (n=1).
b Klippel-Feil (n=2), Down (n=1), Feingold (n=1), Goldenhar (n=1), Opitz (n=1) and SCIMITAR (n=1) syndrome.
c Pathological pH-monitoring (n=30), typical reflux induced lesions during endoscopy (n=19), fundoplication surgery performed (n=18) and clinical significant gastroesophageal reflux but diagnosis unknown (n=4).
d Age 24.7, 43.7, 45.3 and 56.0 years.
e Nissen fundoplication (n=30) and Toupet fundoplication (n=1). Redo-fundoplication was necessary in 6 (19.4%) patients at a median (range) age of 1.0 (0.6-9.2) years. Median (range) time from initial to redo-fundoplication was 0.7 (0.3-8.0) years. Two (6.5%) patients needed a second redo-fundoplication.
f Gastroesophageal reflux symptoms present (n=12). Proton-pump inhibitor (n=13), H2 antagonist ± prokinetic drug (n=4) and prokinetic drug (n=1).

Table 6.2 Endoscopic and histological results from the screening and surveillance program in adult esophageal atresia patients (N=151)

Endoscopy		**n (%)**
Normal esophagus		103 (68.2)
Macroscopic esophagitis [a]	Grade A	8 (5.3)
	Grade B	3 (2.0)
Extension of gastric epithelium above the gastroesophageal junction [b]	with esophagitis Grade A [a]	6 (4.0)
	without esophagitis	31 (20.5)
Other findings	hiatus hernia [c]	97 (64.2)
	inlet patch	17 (11.3)
	recurrent fistula	1 (0.7)
	esophageal varices	1 (0.7)
Histology above the gastroesophageal junction		**n (%)**
Normal mucosa		76 (50.3)
Esophagitis	mild	29 (19.2)
	moderate	4 (2.6)
	eosinophilic	2 (1.3)
Gastric metaplasia	with esophagitis	3 (2.0)
	without esophagitis	
	23 (15.2)	
Intestinal metaplasia	with esophagitis	6 (4.0)
	without esophagitis [d]	4 (2.6)
No biopsies taken [e]		4 (2.6)

a Los Angeles Classification.
b Twenty-nine short-segments of <3 cm and eight long-segments of ≥3 cm. Longest circumferential (C) extent of 7 cm and longest maximum extent (M) of 7 cm.
c Median (range) length of 2 (1-6) cm.
d In the Barrett's mucosa of one patient, epithelial changes indefinite for dysplasia were observed.
e Macroscopic normal esophagus (n=3) and gastric epithelium above the gastroesophageal junction (n=1, C3M3).

RESULTS

From the 289 invited patients 151 (52.2%) were willing to participate the screening and surveillance program. People in the non-participant group were older, with a median age of 38.2 years vs 25.4 years ($p<0.001$). There was no difference in gender. Three patients were not invited, because they had already been diagnosed and treated for cancer in the upper gastrointestinal tract. See flowchart in FIGURE 6.1.

Patient characteristics

A total of 151 patients (85 males) with a median age of 25.4 (range 16.8-68.6) years were included in the program. Dysphagia and GER complaints were reported in respectively 50.3% and 31.1% of the patients. Nine patients (29.0%) who underwent fundoplication surgery had GER complaints. All patients characteristic are depicted in TABLE 6.1.

Endoscopy results

From a total of 158 endoscopies, 147 (93.0%) endoscopies were first surveillance endoscopies. More than half (61.4%) of the upper endoscopies were performed under conscious sedation (midazolam and fentanyl). Columnar-lined esophagus was seen in 37 (24.5%) patients. In eight patients the columnar-lined esophagus extended ≥3 cm above the GEJ with a circumferential extent (C) of 0-7 cm and maximum extent (M) of 3-7 cm. Nodular or other lesions were absent. We saw macroscopic esophagitis in 11 (7.3%) patients (grade A n=8, grade B n=3). In 103 (68.2%) patients no signs of esophagitis or Barrett's mucosa were found. A hiatus hernia was present in 97 (64.2%) patients and an inlet patch in 17 (11.3%) patients. One patient had esophageal varices (grade II according to Paquet's classification26) due to non-cirrhotic portal hypertension caused by a portal vein thrombosis. No squamous lesions were found TABLE 6.2.

Histological results

Of the 37 patients with columnar-lined esophagus, histopathology confirmed IM in ten (6.6%) cases (eight men; median age of 34.0 years), all without dysplasia. Features of the ten patients diagnosed with BE are summarized in SUPPLEMENTARY TABLE 6.3. GM was found in 26 (17.2%) cases (nine men; median age of 25.7 years). In one patient with columnar-lined esophagus no biopsies were taken. Random biopsies above the GEJ revealed active esophagitis in 35 (23.2%) patients: 29 mild esophagitis, four moderate esophagitis and two eosinophilic esophagitis pattern.

Predictors of metaplasia

Compared to patients without metaplasia BE patients had more often undergone esophageal dilations (p=0.04), and had more often a history of fundoplication surgery (p=0.03). Of the 31 patients who underwent fundoplication surgery metaplasia was found in 10 (32.3%; GM=5 and IM=5) patients. Patients with metaplasia were more often diagnosed with hiatus hernia (p=0.06). None of the 18 patients with a gastric pull-up or bowel interposition developed metaplasia TABLE 6.3 .

Univariable logistic regression analysis of observed data (without imputation) demonstrated that fundoplication surgery was significantly associated with BE (OR 4.429; p=0.028) TABLE 6.4 . In the multivariable logistic regression analysis on imputed datasets none of the candidate variables – gender, fundoplication surgery, (prior) use of alcohol, (prior) smoking, age and BMI (based on imputed length/weight) – were associated with metaplasia. Due to the small number of BE cases multivariable analysis to identify risk factors for BE was not feasible.

Gastrointestinal cancer

Four gastrointestinal cancers were diagnosed before the start of the surveillance program. One patient without a history of hereditary colorectal cancer had developed an adenocarcinoma in his coloninterposition at the age of 48 years. Three ESCC were diagnosed in two men at the age of 42 years, 45 years and the latter patient had developed a second ESCC at the age of 60 years in the proximal esophagus, after esophageal resection with gastric tube reconstruction.

The 10-years prevalence of ESCC in EA patients was 685 per 100,000 or 0.7%. Which was significantly higher compared to the general population (aged 17-69 years), with a 10-years prevalence of ESCC of 6 per 100,000 or 0.006% TABLE 6.5 .

Table 6.3 Clinical features of esophageal atresia patients diagnosed with esophageal columnar metaplasia/Barrett's esophagus and without esophageal columnar metaplasia in the screening and surveillance program

Characteristics baseline	No metaplasia (N=114) n (%)	Metaplasia (gastric or intestinal) [a] (N=37) n (%)
Male gender	67 (58.8)	18 (48.6)
Esophageal atresia type A	14 (12.3)	2 (5.4)
Esophageal replacement	18 (15.8)	0
Characteristics or symptoms in history		
Dilation of esophageal stenosis	64 (56.1)	24 (64.9)
≥3 dilation procedures	50 (43.9)	18 (48.6)
Number of dilation procedures; median	1	3
(min; max; IQR)	(0; 15; 0-5)	(0; 35; 0-7)
Fundoplication surgery	21 (18.4)	10 (27.0)
Prior diagnosis of gastroesophageal reflux	55 (48.2)	17 (45.9)
Recurrence of trachea esophageal fistula	9 (7.9)	1 (2.7)
(prior) use of alcohol	76 (66.7)	20 (54.1)
(prior) smoking	25 (21.9)	7 (18.9)
Characteristics at time of first diagnosis of metaplasia/Barrett's esophagus or last diagnosis of no metaplasia		
Age in years; median	25.2	25.9
(min; max; IQR)	(16.8; 57.9; 18.4-36.4)	(17.3; 68.6; 19.7-32.8)
BMI in kg/m^2; median	21.9	21.0
(min; max; IQR)	(15.5; 38.0; 20.0-24.7)	(15.8; 30.9; 19.4-23.6)
Hiatus hernia	66 (57.9)	27 (73.0)
Use of alcohol	74 (64.9)	20 (54.1)
Smoking	24 (21.1)	7 (18.9)
Dysphagia complaints	55 (48.2)	21 (56.8)
Gastroesophageal reflux complaints	31 (27.2)	14 (37.8)
Proton pump inhibitor usage	6 (5.3)	6 (16.2)
Anti-reflux medical therapy	10 (8.8)	8 (21.6)

Non-parametric Mann-Whitney U test for continues variables and Pearson's chi-square test or Fisher's exact test for categorical variables.

a In one patient with columnar-lined esophagus (C3M3) no biopsies were taken. This patient was included in the metaplasia group.

b 'no metaplasia' vs. 'metaplasia'.

c 'no metaplasia' vs. 'Barrett's esophagus'.

p-value [b]	Barrett's esophagus (N=10) n (%)	p-value [c]
0.281	8 (80.0)	0.313
0.361	1 (10.0)	1.000
0.007	0	0.355
0.439	9 (90.0)	0.087
0.635	6 (60.0)	0.303
0.270	5 (0; 35; 2-17)	**0.038**
0.260	5 (50.0)	**0.033**
1.000	7 (70.0)	0.166
0.452	1 (10.0)	0.583
0.128	7 (70.0)	1.000
0.680	2 (20.0)	1.000
0.945	31.6 (17.9; 56.0; 22.8-47.6)	0.189
0.241	20.1 (16.2; 23.6; 16.6-22.5)	0.114
0.057	8 (80.0)	0.153
0.189	7 (70.0)	1.000
0.744	2 (20.0)	1.000
0.385	5 (50.0)	1.000
0.199	2 (20.0)	1.000
0.077	5 (50.0)	**<0.001**
0.078	5 (50.0)	**0.003**

Table 6.4 Univariable logistic regression analysis Barrett's esophagus and metaplasia (gastric or intestinal)

	Barrett's esophagus			Metaplasia		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Male gender	2.806	0.570-13.811	0.204	0.665	0.316-1.400	0.282
Fundoplication surgery	4.429	1.175-16.694	**0.028**	1.640	0.690-3.901	0.263
(prior) use of alcohol	1.105	0.270-4.525	0.889	0.557	0.261-1.190	0.131
(prior) smoking	0.880	0.176-4.411	0.876	0.821	0.322-2.092	0.680
Age in years	1.038	0.987-1.092	0.150	1.002	0.971-1.034	0.905
BMI in kg/m^2	0.755	0.535-1.066	0.110	0.935	0.830-1.052	0.265

Results from analysis of observed data (without imputation).

Table 6.5 Calculation of 10-year prevalence of esophageal squamous cell carcinoma (ESCC)

	Cohort of esophageal atresia patients (aged 17-69 years)	**General Dutch population (aged 17-69 years)**
10-year prevalence of ESCC at January 1 2016	2	772
Number of persons alive at January 1 2016	292 [a]	12,140,743
Calculated 10-year prevalence of ESCC per 100,000 persons	685 (0.7%)	6 (0.006%)

a Untraceable patients were not included.

DISCUSSION

From the 289 EA patients invited 52.2% were willing to participate a surveillance program. In adult EA patients both BE (6.6%) and ESCC prevalence (0.7%) were higher compared to the general population and at a relatively young age. Fundoplication surgery appeared to be the only significant predictor for BE.

In this prospective screening study adult EA patients had a 4-5 fold higher prevalence of BE and at a much younger age compared to the general population, 6.6% (95% confidence interval 3.9-9.4) vs. 1.3%-1.6% with a median age of 31.6 years compared to 57 years in the general population [5, 6]. This high prevalence of BE in EA patients is supported by others (up to 12.5%) [3]. Factors associated with BE and EAC are male gender, older age (≥50 years), white race, tobacco smoking, obesity, hiatus hernia, and GER [27, 28]. In EA patients we found that fundoplication surgery – representing patients with a history of severe GER – was associated with BE in univariable analysis. As BE is thought to evolve from GM we compared patients with

and without metaplasia (GM or IM), but no significant determinants were found. This in contrast to a study in 101 EA patients that showed that long gap, age >30 years, recurrent TEF, esophageal stricture resection during childhood, esophageal stricture in adulthood, and abnormal esophageal manometry were associated with metaplasia [29]. It should be noted that in the above-mentioned study 10/21 patients were defined as having esophageal metaplasia, although no columnar-lined esophagus was observed at endoscopy. Although patients with BE in our study were more likely to have a history of anastomotic strictures, we assume that strictures should not be considered as an independent risk factor for BE. We speculate that patients with anastomotic stricturing more often suffered from GER, which could explain the higher prevalence of BE in this group.

In the general Western population GER complaints have been reported in 10-20% [30]. In studies of EA patients the prevalence ranges widely (18-64%) [3, 31]. The use of different definitions of GER symptoms and the altered perception of esophageal symptoms in EA patients may explain these differences [32]. Moreover, in accordance with previous studies we found a weak correlation between symptoms and endoscopic and histological findings [33, 34]. GER complaints were reported in 31.1% of EA patients. GER was diagnosed endoscopically in 17 (11.3%) patients, but only six patients had symptoms. Fundoplication surgery appeared not to protect against esophageal metaplasia at adulthood. Fundoplication failure has been reported in 15% and pathological pH-metry was found in 43% of EA patients 10-15 years after fundoplication surgery [35, 36]. Wrap failures and children outgrowing their fundoplication may explain these recurrences, especially in EA patients who undergo fundoplication in the first years of life [35].

The high prevalence of BE implies an increased risk to develop EAC in EA patients. In our cohort two men were diagnosed with ESCC prior to the start of our surveillance program, resulting in a 108-fold higher prevalence of ESCC in EA patients compared to the general population. The reason for a possible higher prevalence of ESCC compared to EAC in EA patients is still unknown. EA patients could be at higher risk of developing ESCC than EAC. Or the time needed for EAC to evolve from BE could be longer than our median follow-up time (25.4 years).

Several predictive factors for ESCC have been suggested, such as: low socioeconomic status, tobacco smoking, alcohol consumption, dietary factors, achalasia, and human papilloma virus [28, 37]. In achalasia patients esophageal stasis of food and fluids – causing bacterial overgrowth with nitrosamine production – is thought to increase the risk to develop ESCC [38, 39]. The same pathogenesis might explain ESCC development in EA patients. Several authors have suggested that esophageal strictures requiring dilation procedures predispose for ESCC [9, 10]. Therefore during endoscopic surveillance, the squamous epithelium should be examined in detail, with Lugol's staining to detect early squamous lesions [20].

Esophageal screening for BE and esophageal carcinoma in the general population is not recommended [4, 27]. Our findings may have important implications for the follow-up of EA patients. The high prevalence of BE and ESCC at a young age may warrant lifelong endoscopic follow-up. As many EA patients have dysphagia (48-72%) [40], this may be neglected as an early warning symptom of esophageal cancer in this population. Routine endoscopy in adult EA patients is currently recommended in an ESPGHAN-NASPGHAN guideline [16], but the ideal follow-up schedule has yet to be determined. In our follow-up program all participants – independent of the presence of metaplasia – are advised to undergo endoscopic surveillance, not only to screen for BE and EAC but also for dysplastic squamous epithelium. We recommend to perform chromoendoscopy with Lugol's staining [20] from the age of 25 years onwards to detect superficial ESCC. One could consider to take random biopsies mid-esophageal, preferably from the site of the original TEF or anastomosis. Further long-term prospective cohort studies are needed before a more evidence based cost-effective surveillance program in EA patients can be implemented.

Our study has several limitations. First, the number of patients with metaplasia did not allow identifying clinical predictive factors in multivariable analysis. The response rate in our surveillance program (52.2%) was good, but could be better. Besides age and gender we were not informed about the reason why people did not participate, or were not able to participate because of e.g. disease burden. Second, we included only adults. Although metaplasia has been described in children [41, 42], we believe endoscopies in children should only be performed in high-risk patients. This is supported by the fact that no long segments of BE nor dysplasia was found at the age of 17 years in our follow-up program. Third, the prevalence of histological esophagitis could be misinterpreted as being high as there are no normative data from the general population.

In conclusion, the prevalence of BE and ESCC in young adult EA patients is 4-5 and 108-fold higher compared to the general population. These results warrant uniform surveillance programs for adult EA patients in dedicated centers to facilitate early diagnosis of clinically relevant lesions and prevent death from esophageal carcinoma. As fundoplication surgery in childhood does not seem to protect against esophageal damage in EA patients, these patients should not be excluded from endoscopic surveillance programs.

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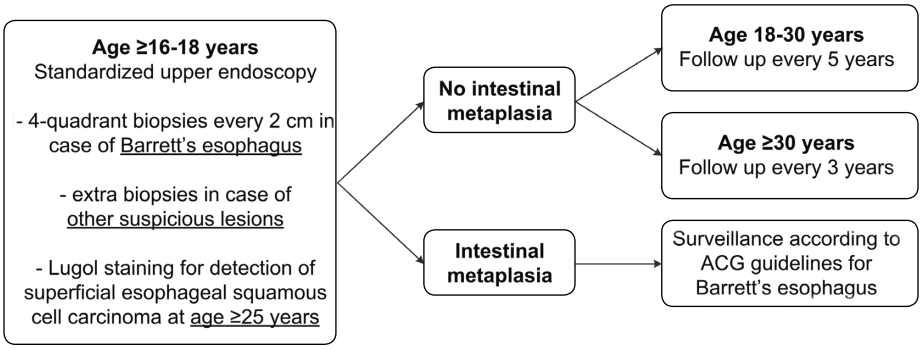

Supplementary figure 6.1 Flowchart of screening and surveillance program in adult esophageal atresia patients.

Supplementary table 6.1 Score for severity of dysphagia complaints

Dysphagia score	
Able to consume a normal diet	0
Dysphagia with certain solid foods	1
Able to swallow semi-solid soft foods only	2
Able to swallow liquids only	3
Unable to swallow saliva (complete dysphagia)	4

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Supplementary table 6.2 Histological evaluation of esophageal biopsies from the gastroesophageal junction

Histopathologic category		Criteria
Normal mucosa		Inflammatory cells within normal limits. No morphological changes, minimal basal hyperplasia or subtle reactive changes
Esophagitis	mild	Slight amount of neutrophils or eosinophils. Elongated papillae, basal hyperplasia, no erosions.
	moderate	Moderate number of neutrophils or eosinophils. Elongated papilla, basal hyperplasia, no erosions.
	erosive	Superficially eroded mucosa, no granulation tissue.
	ulcerative	Deeply eroded mucosa, granulation tissue, prominent epithelial regeneration.
	eosinophilic pattern	Eosinophilia [a] with eosinophilic microabscesses, degranulated eosinophils.
Metaplasia	gastric	Columnar epithelium replacing squamous cell epithelium. Goblet cells absent.
	intestinal	Columnar epithelium replacing squamous cell epithelium. Goblet cells present.
Dysplasia	non	No architectural complexity. Normal maturation as the cells progress toward the mucosal surface.
	low grade	Preservation or only minimal distortion of crypt architecture. Little or no maturation as the cells progress from the crypt bases to the luminal surface.
	high grade	Crypt architectural complexity with irregular, branched, cribriform glands. Absence of maturation, atypia exceeding that of low grade dysplasia: nuclear-to-cytoplasmic ratio, nuclear size, hyperchromasia, polymorphia.
	indefinite	Histologic changes that neither meet the criteria for dysplasia nor for non-dysplasia or absence of representative surface epithelium (technical artifacts).

a Eosinophilia was defined as >15 eosinophils per high-power field.

Supplementary table 6.3 Clinical features of EA patients diagnosed with BE (n=10)

Patient	Surgical history	Medical history before diagnosis of BE
Male 1958 - EA type C - No associated anomalies - No genetic syndrome	- End-to-end anastomosis at day 3. - No fundoplication.	- History of GER unknown. - No esophageal stenosis. - Recurrent bronchitis in childhood.
Male 1959 - EA type C - No associated anomalies - No genetic syndrome	- End-to-end anastomosis at day 3. - No fundoplication.	- History of GER unknown. - Esophageal stenosis at age of 3 months, number of dilations unknown, last dilation at age of 45.3 years: wide proximal esophagus with stricture in distal part. - Recurrent aspirations first 3 years. Recurrent pneumonias child- and adulthood due to aspirations, at age of 27 and 41 years resection of all segments right lower lobe. - Esophageal manometry (age 13.3 years): 100% non-transmitted, inactive motor function.
Male 1962 - EA type C - No associated anomalies - No genetic syndrome	- End-to-end anastomosis at day 1 with tension at anastomosis. - Reconstruction of the angle of His with correction of a hiatus hernia at age 2.8 years.	- Clinically significant GER since age of 2.8 years. - Esophageal stenosis in childhood, multiple dilations. - At age 33.4 years endoscopic sclerosis of arterial bleeding from Mallory–Weiss tear in distal esophagus.
Male 1965 - EA type C - No associated anomalies - No genetic syndrome	- End-to-end anastomosis at day 3 with slight tension at anastomosis. - Resection of stenotic anastomosis at age of 3 months. - No fundoplication.	- Clinically significant GER since age of 8 years. - No esophageal stenosis. - At age of 32.9 years reflux esophagitis grade B. Extension of gastric epithelium above the GEJ with gastric metaplasia without dysplasia at histological examination at age of 36.2, 40.2, and 42.6 years.
Female 1977 - EA type C - Vertebral anomalies, partial AVSD, duodenal stenosis, jejunal stenosis. - No genetic syndrome	- End-to-end anastomosis with Livaditis procedure at day 1. - Nissen fundoplication at age 4.7 years. - Resection of strangulated ileum at age of 1 month.	- Clinically significant GER since birth. - Esophageal stenosis at age of 3 months, 25 dilations, last dilation at age of 5 years. - Endoscopic removal of food stuck in the esophagus twice before the age of 4 years. - At age of 4 years reflux esophagitis. Extension of gastric epithelium above the GEJ (C8M8) with gastric metaplasia without dysplasia at histological examination at age of 19.5, 20.5 and 22.4 years.

Features at diagnosis of BE	BE diagnosis
- Symptoms: dysphagia grade I, seldom food impactions, non-cardiac chest pain. - Allergy: none. - Medication: none. - Intoxications: Alcohol ≤7 units/week. Non-smoking. - Family history: negative for cancer.	- Age at time of diagnosis 56.0 years. C3M3, no focal lesions, no dysplasia. Hiatus hernia (3 cm). Follow-up: - Last evaluation of BE at age of 58.6 years: C3M3, no focal lesions, indefinite for dysplasia.
- Symptoms: dysphagia grade I, seldom food impactions, seldom respiratory tract infections. - Allergy: birch. - Medication: PPI. - Intoxications: Alcohol ≤7 units/week. Non-smoking. - Family history: father bladder cancer at age of 72 years, sister rectal cancer at age of 52 years.	- Age at time of diagnosis 45.3 years. C2M2, no focal lesions, no dysplasia. Hiatus hernia (2 cm). Follow-up: - Last evaluation of BE at age of 55.9 years: C2M3, no focal lesions, no dysplasia.
- Symptoms: dysphagia grade I, food impactions once a week, regurgitation and heartburn. - Allergy: none. - Medication: PPI. - Intoxications: No alcohol . Non-smoking. - Family history: negative for cancer.	- Age at time of diagnosis 54.5 years. C0M1, no focal lesions, no dysplasia. Hiatus hernia (4 cm).
- Symptoms: dysphagia grade I, no food impactions. - Allergy: none. - Medication: PPI. - Intoxications: Alcohol ≤7 units/week. Non-smoking. - Family history: unknown.	- Age at time of diagnosis 43.7 years. C0M2, no focal lesions, no dysplasia. Hiatus hernia (2 cm). Follow-up: - Last evaluation of BE at age of 51.7 years, C0M2, no focal lesions, no IM in biopsy, no dysplasia. Reflux esophagitis grade A. Hemorrhagic gastritis. - Esophageal stenosis at age of 44.1 years, 3 dilations, last dilation at age of 45.2 years. Dysmotility proximal esophagus, no obstruction.
- Symptoms: dysphagia grade I, seldom food impactions. - Allergy: latex, plasters, dust mites. - Medication: PPI. - Intoxications: No alcohol. Non-smoking. - Family history: unknown.	- Age at time of diagnosis 24.7 years. C8M8, no focal lesions, no dysplasia. Follow-up: - Last evaluation of BE at age of 36.7 years. C5M5, no focal lesions, no dysplasia, at 25 cm mild esophageal stenosis

Patient	Surgical history	Medical history before diagnosis of BE
Male 1981 - EA type C - No associated anomalies - No genetic syndrome	- End-to-end anastomosis at day 0. - Recurrent TEF at of age 4 months. - Nissen fundoplication at age 1 years and re-Nissen at age of 9.2 years.	- Clinically significant GER since birth, at age 9 years recurrence of GER despite Nissen fundoplication. - No esophageal stenosis. - At age 9 years reflux esophagitis.
Male 1986 - EA type C - Anorectal malformation with accompanying hypospadias, renal agenesis, duplicated ureter - No genetic syndrome	- End-to-end anastomosis at day 1 with slight tension at anastomosis. - No fundoplication. - Kidney transplants at age 2, 22 and 28 years for end-stage kidney failure.	- Clinically significant GER at age 10 months, at age 22.9 and 23.9 years ulcerative esophagitis (grade unknown, no microorganism), start PPI. - Esophageal stenosis at age 1 month, 21 dilations. Second erosive and ulcerative stricture at age 22.9 years, 35 dilations.-Tracheomalacia, frequent lower respiratory tract infections.
Male 1989 - EA type C - Vertebral anomalies, pyloric stenosis - Klippel-Feil syndrome	- End-to-end anastomosis at day 2. - Pyloromyotomy at age of 2 months. - Nissen fundoplication at age of 2 months and re-Nissen at age of 11 months.	- Clinically significant GER since birth, at age of 11 months recurrence of GER despite Nissen fundoplication. - Esophageal stenosis at age of 1 month, 9 dilations, last dilation at age of 11 months. - At age of 11 months reflux esophagitis grade B.
Female 1992 - EA type C - Muscular VSD - No genetic syndrome	- End-to-end anastomosis at day 1 with slight tension at anastomosis. - No fundoplication.	- No history of GER. - Esophageal stenosis at age of 1 month, 3 dilations, last dilation at age of 2 months - Endoscopic removal of food stuck in the esophagus at age of 4 and 13 years. - Tracheomalacia, frequent lower respiratory
Male 1997 - EA type A - No associated anomalies - No genetic syndrome	- Gastrostomy at day 2. End-to-end anastomosis at day 52. - Nissen fundoplication at age 6 months.	- Clinically significant GER at age 5 months. - Esophageal stenosis at age 3 months, 6 dilations, last dilation at age of 6 months. - PEP mask for severe tracheomalacia. Complaints of pain, probably due to esophageal spasm.

AVSD: atrioventricular septal defect, BE: Barrett's esophagus; EA: esophageal atresia; GEJ: gastroesophageal junction, GER: gastroesophageal reflux; IM: intestinal metaplasia; PPI; proton pump inhibitor; TEF: trachea-esophageal fistula; VSD: ventricular septal defect.

Features at diagnosis of BE	BE diagnosis
- Symptoms: dysphagia grade I, no food impactions. - Allergy: none. - Medication: none. - Intoxications: Alcohol ≤7 units/week. Active smoking. - Family history: unknown.	- Age at time of diagnosis 32.4 years. C2M3 with ulcerative esophagitis, no focal lesions, no dysplasia, at 25cm villous polyp (squamous papilloma). Hiatus hernia (4 cm).
- Symptoms: no dysphagia, no food impactions. - Allergy: none. - Medication: PPI. - Intoxications: No alcohol. Non-smoking. - Family history: negative for cancer.	- Age at time of diagnosis 30.7 years. C0M5, semi-circular, no focal lesions, no dysplasia. Hiatus hernia (2 cm).
- Symptoms: no dysphagia, no food impactions. - Allergy: none. - Medication: none. - Intoxications: Alcohol ≤7 units/week. Non-smoking. - Family history: negative for cancer.	- Age at time of diagnosis 23.4 years. C2M6, no focal lesions, no dysplasia. Wide open pylorus. Hiatus hernia (3 cm). Follow-up: - Last evaluation of BE at age of 27.0 years. C2M5, no focal lesions, no dysplasia.
- Symptoms: no dysphagia, seldom food impactions. - Allergy: none. - Medication: none. - Intoxications: Alcohol ≤7 units/week. Former smoking (quit at age of 19 years). - Family history: grandfather colorectal cancer at age of 67 years.	- Age at time of diagnosis 20.9 years. C0M2, no focal lesions, no dysplasia. No hiatus hernia. Follow-up: - Last evaluation of BE at age of 23.9 years. C0M1, no focal lesions, no IM in biopsy, no dysplasia.
- Symptoms: no dysphagia, no food impactions, at least once a month chest pain during exercise. - Allergy: none. - Medication: none. - Intoxications: Alcohol ≤7 units/week. No smoking. - Family history: unknown.	- Age at time of diagnosis 17.9 years. C0M0.5, no focal lesions, no dysplasia. Hiatus hernia (3 cm).

7

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

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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.

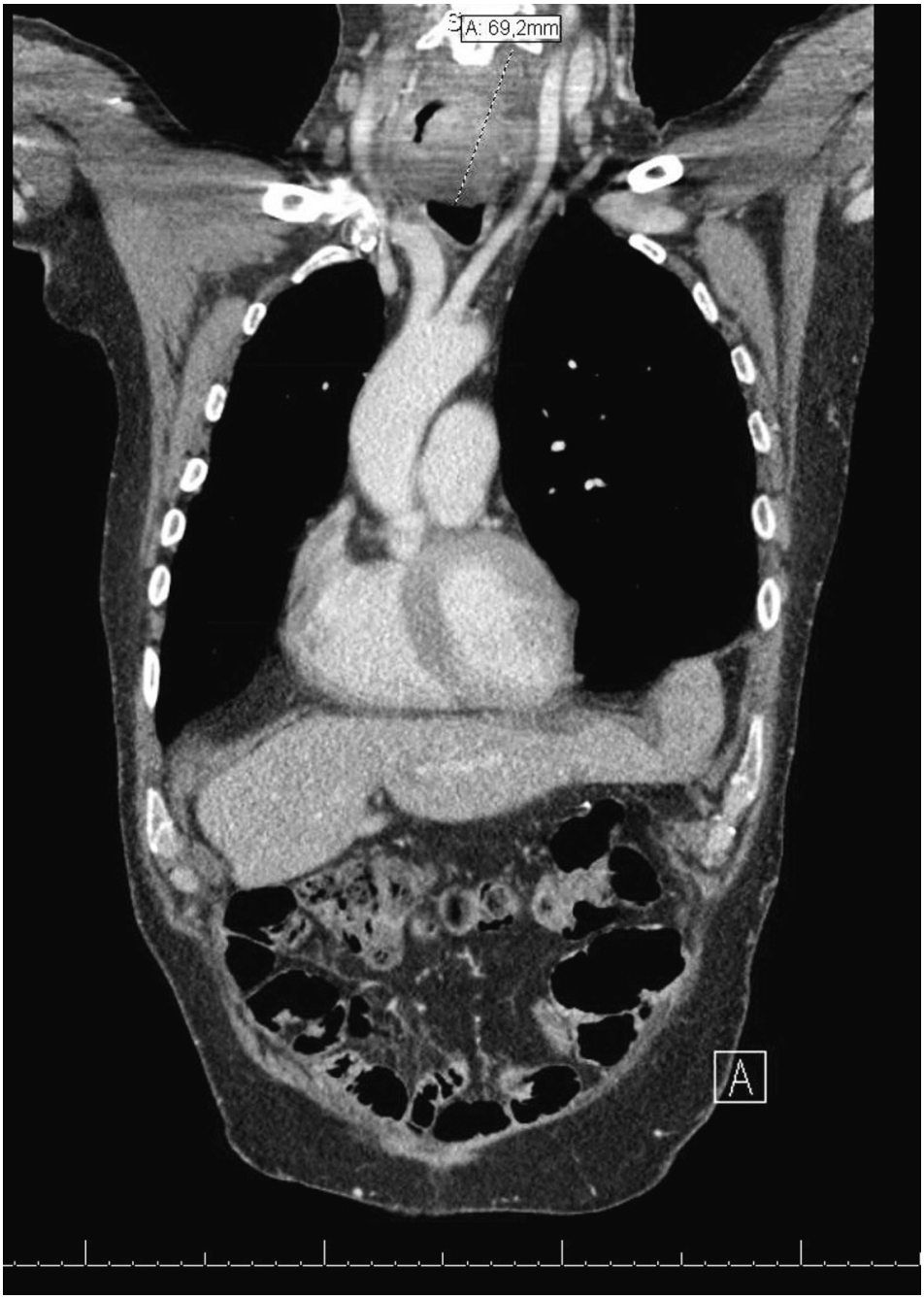


Figure 7.1 Chest computed tomography scan (CT scan) (case 1, tumor 2) demonstrating a tumor mass in the cervical native esophagus with suspected tumor invasion in the left thyroid gland.

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.

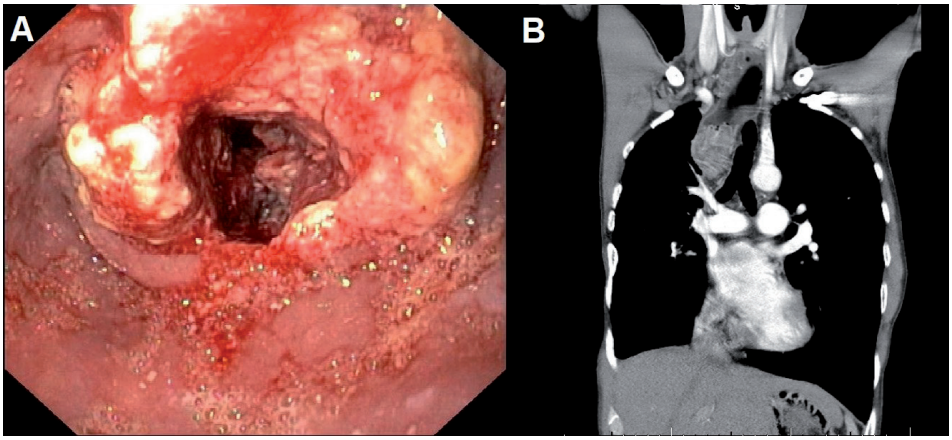
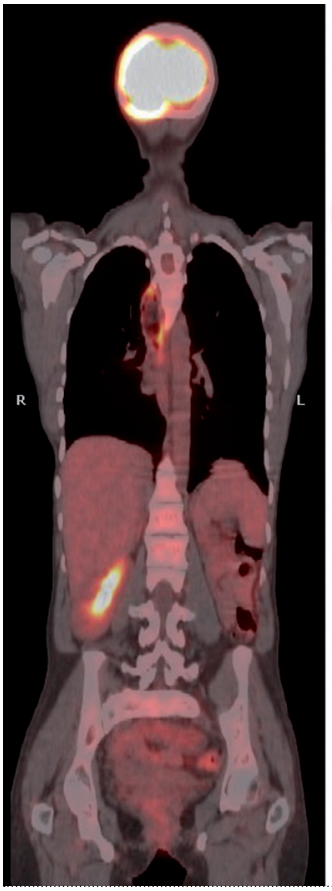


Figure 7.2
Findings at upper endoscopy and chest computed tomography scan (CT scan) (case 2).
A: Upper endoscopy revealing a stenotic ulcerative tumor in the proximal esophagus, 22-29 cm from incisors. Histological examination of esophageal biopsies confirmed the diagnosis esophageal squamous cell carcinoma.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



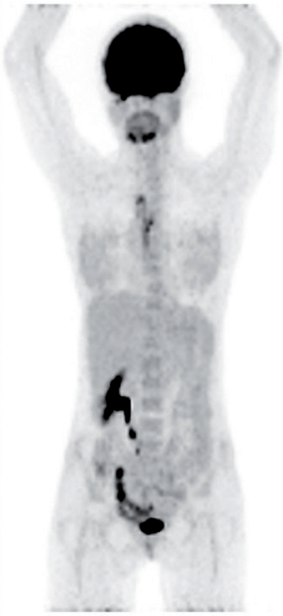


Figure 7.3
Initial findings at positron emission tomography-computed tomography scan (PET-CT scan) (case 3), showing PET-positive lesion in the distal esophagus without metastasis.

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.

At presentation the patient suffered from pneumonia with a density in the lower lobe of the right lung. Subsequent PET-scan revealed a PET-positive thickening in the colonic interposition for which he had been referred to our center. He complained about progressive dysphagia without any weight loss (BMI 18.6 kg/m²). He was a cannabis smoker (2 joints/wk), had quit tobacco smoking just before presentation (a few cigarettes per day) and only sporadically drank alcoholic beverages. Upper endoscopy revealed the proximal and distal anastomosis of the colonic interposition at, respectively, 21 and 47 cm from incisors. From 26-30 cm from incisors a tumor was visible in the colon interposition which could be easily passed with the scope. Histology revealed a moderately differentiated adenocarcinoma. No abnormalities were found at colonoscopy. PET-CT scan showed circumferential thickening of the colonic interposition over a length of 10 cm, not clearly separated from the thyroid and left brachiocephalic vein, a small lesion in the lower right lobe of the lung (PET-negative) and a few locoregional lymph nodes (≤ 1 cm, PET-negative) FIGURE 7.4A AND 7.4B.

Patient D was treated with induction chemotherapy (capecitabine/oxaliplatin) to enable maximum tumor regression. After six treatments, the colonic interposition was resected and an esophagostomy and jejunal fistula for feeding were created. Pathological examination confirmed the diagnosis of colonic adenocarcinoma with a maximum diameter of 4.1 cm, tumor free resection margins (≥ 1 cm) and one of 19 lymph nodes positive for metastasis (ypT2N1). Family history was negative for Lynch Syndrome. Both pentaplex microsatellite instability testing and mismatch repair gene expression analysis for MLH1, MSH2, MSH6 and PMS2 were normal.

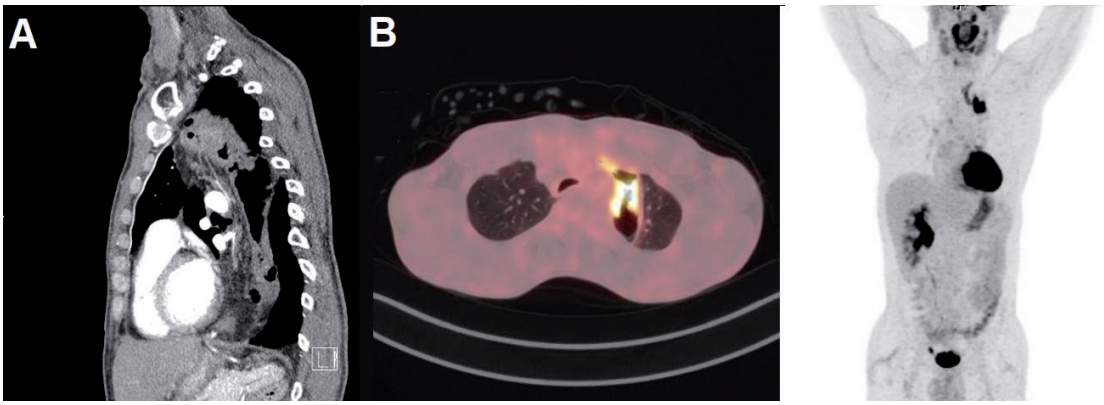


Figure 7.4
Initial findings at positron emission tomography-computed tomography scan (PET-CT scan) (case 4).
A: Chest CT scan image with a circumferential wall thickening of the thoracic colonic interposition over a length of 10 cm, not clearly separated from the thyroid and left brachiocephalic vein. Locoregional suspected lymph nodes (< 1 cm).
B: PET-CT scan showing a PET-positive lesion in the thoracic colonic interposition. No PET-positive lesions or lymph nodes.

After 4 mo continuity was restored by a subcutaneous gastric tube pull-up. At oncological follow-up one year after resection of the colonic interposition patient D did not experience any dysphagia, weight was stable (BMI 19.7 kg/m2) and ultrasound of the liver and CEA were normal (2.72 µg/L).

DISCUSSION

We presented four cases of gastrointestinal cancer that have developed more than 30 years after surgical treatment of EA: three esophageal carcinoma and one unusual presentation of colorectal carcinoma in a colonic interposition. These patients' relatively young age, the fact that only few carcinogenic factors were identified and the high incidence of cancer development in a low prevalence disease suggest that EA carries an increased risk for esophageal cancer development and therefore screening and surveillance may be warranted, as recommended in the ESPGHAN-NASPGHAN guideline [11].

Esophageal cancer is the 8th most common cancer worldwide, with an incidence rate of 6.4 and 1.2 per 100,000 males and females, respectively, in developed countries and 10.1 and 4.1 per 100,000 males and females, respectively, in less developed countries [17]. ESCC and EAC have different etiologies. ESCC arises from dysplastic squamous epithelium and is associated with a low socioeconomic status, use of tobacco or alcohol, several dietary factors, and human papilloma virus [18, 19]. The main risk factors for EAC are GER, use of tobacco, obesity, and hiatal hernia [18]. Chronic GER might lead to gastric and intestinal metaplasia of the squamous epithelium in the esophagus, known as Barrett's esophagus, which predisposes to dysplasia and EAC. GER is present in up to 67% of the adult EA patients and is likely to contribute to EAC development [5]. However, in literature – and also in our case series – ESCC is more common than EAC in EA patients [10, 12-15]. The reason for this high risk of ESCC development has not yet been estabilised. The pathogenesis might be the same as in achalasia, where ESCC is thought to result from stasis, causing bacterial overgrowth with nitrosamine production and subsequent esophageal inflammation, dysplasia and cancer [20, 21]. Most of the ESCC in EA patients were found near or at the anastomosis (mid-distal esophagus). It has been suggested, therefore, that frequent dilation procedures with associated mucosal tears, scarring and inflammation may lead to development of ESCC in this patient group [10, 12]. Mitomycin-C, an antifibrotic applicant used to prevent recurrence of strictures, may be an additional risk factor for ESCC, but this was not used in any of the patients in present case series [22]. Moreover, genetic predisposition may contribute to esophageal cancer in EA patients and is subject to future studies.

Endoscopic surveillance of EA patients is advocated to detect lesions at an early stage [11]. Those treated with a colonic interposition should not be excluded from surveillance, as carcinoma could arise in the cervical native esophagus or thoracic colon. More data on the actual incidence of esophageal cancer development in adulthood will hopefully become available soon when surveillance programs have been implemented. Together with the identification of risk factors this will help to optimize surveillance strategies in EA patients. Until then, pediatric surgeons and gastroenterologists who are involved in treatment of EA patients should be made aware of the cancer risk and be encouraged to reach consensus on optimal surveillance. When EA patients reach adulthood, they should be transferred to a gastroenterologist for endoscopic surveillance.

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8

General discussion

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.

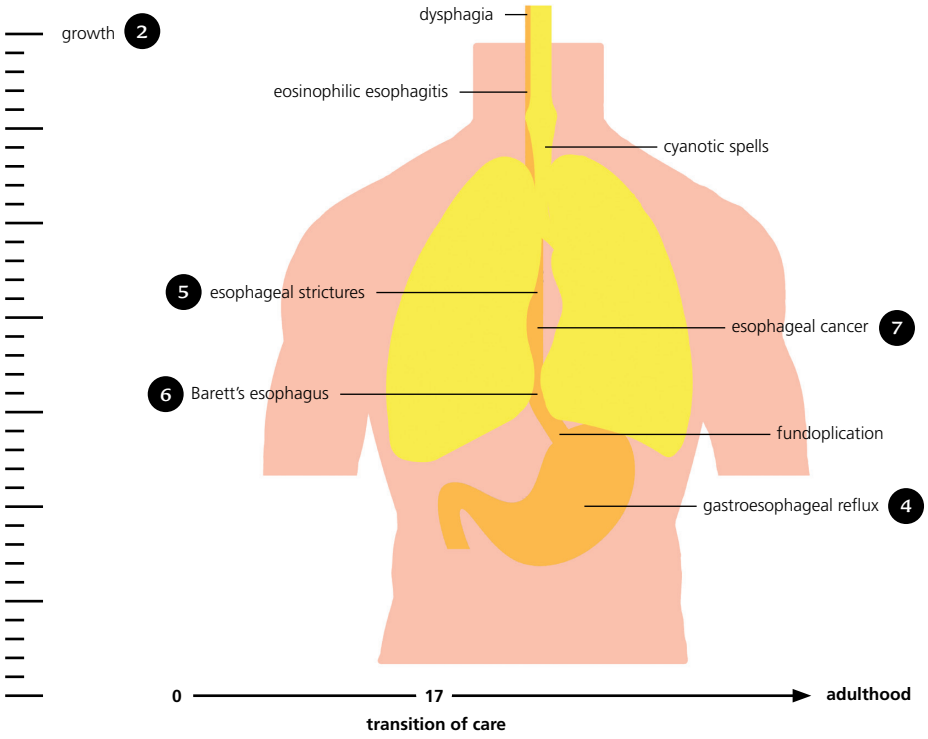

Figure 8.1 Gastrointestinal and nutritional complications in esophageal atresia patients.

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)

in the first five years of age with catch-up growth between two and five years [29, 30]. In Chapter 2 we longitudinally evaluated growth in children born with EA up to the age of 12 years. Up to the age of five years, these children had a significantly lower weight (weight-for-height) compared to the general population. Height (height-for-age) was significantly lower up to the age of eight years. At 12 years of age weight and height had normalized. In the future, we will continue to follow this group during adolescence to evaluate whether nutritional intervention is needed to obtain a normal growth spurt in puberty.

Target height and its SD score (SDS) can be calculated with parental heights [31]. This can be useful to discriminate the influence of disease on growth [32]. When we corrected height for individual target height, the SDS for height (SDS for distance-to-target-height) improved in our study. This finding shows the importance of structurally recording parental height, as a child's nutritional status can be underestimated when only interpreting SDS for height-for-age.

Previous studies found several explanatory variables for growth impairment in EA patients, such as long-gap EA, esophageal substitution, and a history of GER [12, 21, 22]. In Chapter 2 we also evaluated these factors, but did not find associations with growth impairment. We found two of the studied explanatory variables to be negatively associated with growth: low birthweight and a history of fundoplication surgery. Children with a low birthweight were more likely to have a short stature and to be underweight, this was previously described by others [15]. Fundoplication surgery was mostly performed before the age of six months. Many children who underwent fundoplication surgery had height and weight below the reference norm after surgery. We suspect that these children have persistent feeding problems preventing catch-up growth. Moreover, they may have had more extreme disease severity posing a risk for failure to thrive. The SDS weight-for-height of these children increased from 1-2 years, which we assume can be ascribed to adequate treatment of severe GER.

We found that number of surgeries and history of pulmonary infections were positively associated with weight (weight-for-height) in EA patients. We speculate that children with recurrent hospitalizations more often received dietary interventions. In congenital diaphragmatic hernia patients close involvement of multidisciplinary nutrition support teams was indeed found to prevent failure to thrive [33]. It is worth recommending to have such teams, including dieticians and speech-language pathologists, available to support hospitalized children in general, and continue supporting high-risk-patients after discharge to home. These multidisciplinary teams can optimize nutritional status in early years, which is crucial for normal brain and immune system development [7, 8]. Future multicenter studies should focus on optimization of nutritional intake and on the effects of growth problems on brain development and school performance in this population.

Prevalence and risk factors of gastrointestinal problems in esophageal atresia patients

Gastroesophageal reflux

GER is a physiologic phenomenon. When GER causes troublesome symptoms interfering with daily life or complications it is referred to as GER disease (GERD) [34]. GERD – a motility disorder – is common (up to 67%) in EA patients, both in early childhood and adulthood [4, 35]. It results in respiratory and gastrointestinal problems in the short and long term, e.g. aspiration pneumonia, apparent life-threatening events, dysphagia, feeding problems, chronic respiratory symptoms, esophageal strictures, esophagitis, BE and esophageal cancer [4, 36-39]. Given the high prevalence of GERD, early diagnosis and management of GERD is important to reduce GERD associated morbidity.

When GERD is clinically suspected, several diagnostic tools can help to diagnose GERD: e.g. barium imaging, esophagogastroduodenoscopy, manometry, scintigraphy, pH monitoring, and combined pH and impedance (pH-MII) monitoring. pH monitoring detects pH changes of esophageal contents, but lacks the ability to detect weakly and non-acid boluses [40]. pH-MII monitoring can detect both acid and non-acid reflux, but is not available in all medical centers and underestimates GER events in patients with esophagitis or motility disorders as a result of low baseline impedance values [34, 41-43]. Besides, reference values are lacking and inter- and intra-observer agreement studies show diverging results [44-47]. Because of this, the recent ESPGHAN-NASPGHAN Guideline on pediatric GERD (2018) dissuades use of pH-MII monitoring alone for diagnosing GERD in infants and children [34]. It should only be considered to 1) correlate persistent symptoms with (non-)acid GER, 2) evaluate the role of (non-)acid GER in esophagitis and other symptoms suggestive for GERD, 3) determine the efficacy of anti-acid therapy, and 4) differentiate children with hypersensitive esophagus, functional heartburn and non-erosive reflux disease [34].

Although many children with EA are exposed to chronic GER, only a few experience troublesome symptoms. Both pH-MII monitoring results suggestive for GERD and endoscopic abnormalities have been described in asymptomatic children with EA [48-51]. The discrepancy between symptoms and GER makes it difficult to decide in which patients GER should be monitored. The ESPGHAN-NASPGHAN Guideline (2016) for EA patients recommends to routinely treat all EA patients with anti-acid treatment in the neonatal period and to monitor GER using pH-MII monitoring and/or endoscopy at time of discontinuation (regardless of symptoms) and during long-term follow-up in symptomatic children with EA [4].

In Chapter 4 we evaluated GER symptoms in 8-year old children with EA using the GER questionnaire developed by Manterola et al. [52]. The questionnaire was suggestive for GERD (score >3) in 29% (n=7), but in only two of these children a high reflux index (>7%) was found. pH-MII parameters were similar in children with low and high Manterola scores. This may have been the result of day-to-day variability of pH-MII measurements in EA patients, or perhaps disturbed impedance patterns make pH-MII studies unsuitable for GER detection in EA patients [53]. Dysphagia – which may be associated with dysmotility, eosinophilic esophagitis or strictures rather than GER – was mentioned by 5/7 children. Regurgitation was scored in 6/7 children with a high Manterola score, which – in children with EA – can also be regurgitation from the esophagus rather than the stomach. It may therefore be that the Manterola questionnaire is not suitable for EA patients. Development of an appropriately validated questionnaire for children with EA to determine which child benefits from preventive measures to prevent complications from GER (e.g. acid-suppression, prokinetics, fundoplication) and how is important.

Reference values for pH-MII monitoring in symptomatic children without EA have been published, but due to ethical issues true normal values in healthy asymptomatic children cannot be established [54-57]. Several groups have reported their experiences with pH-MII monitoring in post-EA repair children of different ages, but cut-off values for pathological results remain unknown [48, 49, 58-63]. Moreover, differences in study protocols makes comparing results difficult.

Bolus retention, abnormal motility patterns during swallowing and decreased baseline impedance caused by GER and dysmotility are frequently observed in EA patients. As these can disturb automated reflux detection in pH-MII measurements, manual evaluation of bolus events is necessary for accurate identification of GER in EA patients.

In Chapter 4 we evaluated acid and non-acid GER in 57 EA patients aged ≤18 months and 8-years old using pH-MII monitoring. All reflux events were manually reviewed and modified or deleted in case of incorrect identification of the reflux event. In both infants and school-aged children non-acid and mixed refluxes were more frequently observed than acid and liquid refluxes, respectively. We found similar results for reflux index (acid exposure index (%)), number of retrograde bolus movements (RBM) and bolus clearance time compared to available reference values in children without EA (asymptomatic neonates or children with gastrointestinal, pulmonary or neurological symptoms) [54, 56, 57, 64]. Compared to available pH-MII results in children born with EA, number of RBM in our cohort of infants was high compared to a small Dutch cohort [58], but similar to other cohorts [48, 63]. Results in 8-year old children were comparable. We found a lower reflux index compared to most cohorts of EA patients: 2.6% vs 5.8-6.1% in infants [62, 63] and 0.3% vs 2.5-8.3% in older children [49, 60, 61].

We found a large overdetection of reflux events in automated analysis of pH-MII measurements in EA patients. After manual evaluation 39% of reflux events was deleted from the tracings. These were mainly non-acid swallows which the software incorrectly identified as reflux events. We found two main reasons for modification of retrograde boluses after visual evaluation: correction of incorrect identification of proximal bolus events and correction of bolus clearance time. The software misclassified swallows to clear retrograde boluses as proximal boluses. This was caused by air in the esophagus after a swallow. In several children, stasis of fluids was present in channel Z3 and Z4, at the level of the esophageal anastomosis. The software did not recognize this stasis and measured a shorter bolus clearance time. This was also observed in 118 adults (without EA) with endoscopy-negative heartburn [65]. This raises the question whether automated analysis is accurate enough to identify GER in EA patients. We believe the percentage of overdetection of reflux events in automated analysis of pH-MII measurements in EA patients is too high to ignore and to perform automated analyses without manual revision. Manual revision, however, carries the risk of greater inter-observer variability. Refinement of automated software is needed to identify impedance reflux patterns in patients with complex motility disorders such as EA.

Although the ESPGHAN-NASPGHAN Guideline for EA patients recommends to prescribe anti-acid therapy in all neonates with EA, a recent systematic review found prophylactic anti-reflux treatment not to prevent stricture formation after EA repair (low quality of evidence) [4, 66]. As described in Chapter 4, reflux in EA patients is mainly non-acid. An Italian study found that symptoms in infants (<12 months) were mainly associated with non-acid reflux, while symptoms in older children were mainly caused by acid reflux [62]. Currently there are no effective medications available to treat non-acid GER in children. A small double-blinded placebo RCT in children without EA showed that Baclofen inhibits transient lower esophageal sphincter relaxation and accelerates gastric emptying, but is dissuaded in guidelines as a first-choice therapy in children because of known side effects in adults [34, 67]. Future studies in EA patients assessing the usefulness of anti-acid therapy in preventing complications from GER are needed.

Surgical intervention (e.g. fundoplication surgery) is considered when medical therapy fails in children with severe GERD. The recent clinical Guidelines for the diagnosis and management of GERD in children recommend to consider anti-reflux surgery in children with GERD and one of the following: 1) life threatening complications of GERD after failure of optimal medical treatment; 2) symptoms refractory to optimal therapy after appropriate evaluation to exclude other underlying diseases; 3) chronic conditions with a significant risk of GERD-related complications; or 4) the need for chronic pharmacotherapy for control of signs and/or symptoms of GERD [34]. However, no controlled trials have been published to evaluate the role of anti-reflux surgery in EA patients. In EA patients with esophageal dysmotiliy, surgical intervention might worsen stasis of food and fluids. Studies in patients without EA have

shown that fundoplication surgery does not necessarily protect against aspiration pneumonia [68, 69]. The Guideline for EA patients states that EA patients – despite the risk of post-fundoplication complications – might benefit from anti-reflux surgery, especially those with severe refractory esophageal strictures [4]. Future controlled trials should focus on the role of fundoplication surgery in EA patients.

Anastomotic strictures

Anastomotic stricture formation is the most frequent post-operative complication after EA repair (17%-59%), occurring mostly in the first year of life [70, 71]. Several factors are thought to contribute to stricture formation after EA repair, such as long gap EA with consequent anastomotic tension, anastomotic leakage and GER [71-79]. These anastomotic strictures should not be confused with congenital esophageal stenosis, which are frequently found in neonates born with EA (3%-47% compared to 1:25,000/1:50,000 in the general population), but have a different etiology [4].

In Chapter 5 we describe a large multicenter study in 454 Dutch children born with EA (median follow-up of 6.6 years; range 0.6-16.9 years). Dilations of an anastomotic stricture were performed in 58% of children. Reported incidence rate of strictures after EA repair ranges widely (9%-79%) [80]. A uniform definition of an esophageal stricture after EA repair is lacking, which makes it difficult to compare the results between studies.

An esophageal stricture is mostly defined as any narrowing of the esophagus requiring at least one dilation [71, 76, 77]. However, definitions vary based on frequency of dilations [81-86], luminal diameter [73], or symptomatology [72, 75]. In several centers clinicians decide to surgically intervene already after three consecutive dilation procedures. Because of this, a clinically significant esophageal stricture is often defined as a stricture requiring ≥3 or ≥4 dilations [84-86]. Based on the definition in the international Guideline on pediatric endoscopy, we defined the following definition of a refractory esophageal stricture: an anastomotic stricture requiring ≥5 dilations at maximally four-week intervals [87]. This definition distinguishes *refractory* strictures from so called *recurrent* strictures. In our study we found refractory strictures of an end-to-end anastomosis in 7.3% of children. Isolated EA, anastomotic leakage and early stricture (≤28 days after anastomosis) were associated with refractory stricture development.

Others also found isolated EA to be associated with stricture formation [72-74]. The large esophageal gap often requires staged surgery or esophageal replacement (e.g. gastric pull-up, jejunal/colonic interposition). Although primary repair of a large gap is thought to result in anastomotic tension with subsequent stricture formation, literature is contradictory [83, 88]. Current practice in children born with an isolated EA is performing a primary anastomosis of the esophagus. In our study, we found a high percentage of refractory strictures in these

children (27%), which is important information for pre-operative parental counseling.

We believe that anastomotic leakage enhances inflammation and scarring of the anastomotic area, with subsequent stricture formation. This association was also found by others [78, 79].

We found esophageal dilation within 28 days postoperatively ('early stricture') to be associated with refractory strictures. A possible explanation is that more severe (refractory) strictures may occur in the first weeks after esophageal anastomosis. However, in those first weeks postoperatively the anastomosis is still vulnerable and early anastomotic dilation might be an independent risk factor for refractory strictures. Our data did not allow to draw any conclusions on this subject. Most refractory strictures developed within four months postoperatively. We assume that refractory strictures after this period ('late onset') are related to altered food consistency as more solid formulas can cause dysphagia, food impaction, stasis, aspiration or vomiting.

We hypothesized that thoracoscopic EA repair increases refractory esophageal stricture formation, however we could not confirm this in our study (only 54 thoracoscopic procedures in two centers). In thoracoscopic EA repair visualization is better and the dissection is usually more limited compared to open corrections. A recent study found thoracoscopic and staged EA repair to be associated with clinically relevant stricture formation (≥4 dilations) [85], however two reviews found comparable stricture rates after open and thoracoscopic EA repair [89-91].

Another factor thought to increase esophageal stricture formation is anastomotic tension [72, 74-78]. Since anastomotic tension is a subjective observation which is often poorly documented in surgery reports, we choose to include anastomotic leakage as a predictor for refractory strictures in our study instead.

Although others have identified GERD as a risk factor for esophageal stricture development [71, 74, 78, 79], studies in EA patients have shown that prophylactic anti-acid therapy did not always protect against stricture development [92-94]. Moreover, studies are hard to compare since different protocols and definitions are used. In our study anti-reflux surgery was more frequently performed in patients with a refractory stricture. This surgery should be considered as being a therapeutic intervention rather than a risk factor for stricture development, since it was mostly performed after a refractory stricture had developed.

Although literature on esophageal stricture formation in EA patients is scarce, other reported risk factors for post EA repair stricture development are prematurity, birthweight and cardiac anomalies [72, 85, 93]. We could not confirm this in our study.

Future studies can hopefully answer the question whether adequate acid suppression aiming to protect the anastomotic area in high risk patients (e.g. children with isolated EA, anastomotic leakage, early strictures) is effective in reducing refractory stricture formation. Multicenter studies focusing on adjuvant treatments for esophageal strictures (e.g. stent placement, intralesional steroids injection, mitomycin C application, endoscopic needle knife incision and resection surgery) are needed to evaluate the effectiveness of these methods in reducing refractory stricture development. To compare results from different studies, we recommend to use a uniform definition for refractory anastomotic strictures: 'an anastomotic stricture requiring ≥5 dilations at maximally four-week intervals'.

Esophagitis and Barrett's esophagus (BE)

Chronic GER may lead to esophageal mucosal damage such as esophagitis and BE, which are both frequent in EA patients. During endoscopy esophagitis is found in 25.1% of EA patients (12%-15% in general population)(see overview of literature in Chapter 2) [95, 96]. BE is diagnosed if gastric epithelium is observed in the esophagus and metaplasia is confirmed in the biopsy [97]. In accordance with the ACG guidelines (2008), we considered the presence of goblet cells – present in intestinal metaplasia (IM) and absent in gastric metaplasia (GM) – obligatory to confirm the diagnosis of BE although malignant transformation in GM has been described [97].

In the general adult population the prevalence of BE is 1.3%-1.6% and is predominantly diagnosed in middle-aged white males [95, 98, 99]. In EA patients BE is described in up to 12.5% [35]. Since BE is a premalignant lesion which predisposes to esophageal adenocarcinoma (EAC) with an annual risk of 0.5%, endoscopic surveillance in EA patients was recently recommended in an ESPGHAN-NASPGHAN guideline (2016) [4, 100].

In Chapter 6 we describe the first results of a screening and surveillance program in adult EA patients. Since 2013, all EA patients aged 17 years or older have been referred to the Gastroenterology department of our center for endoscopic screening and surveillance of the esophagus. From the 289 invited EA patients, 151 (52%) were willing to participate in the surveillance program. We found a prevalence of BE (IM) of 6.6%, which is 4-5 fold higher compared to the 1.3%-1.6% in the general population population [95, 98].

In the general population BE is associated with several risk factors such as male gender, older age (≥50 years), white race, tobacco smoking, obesity, hiatus hernia, and GER [101, 102]. In the general population BE is diagnosed at a median age of 57 years [95, 98]. We found BE at a much younger age (median of 31.6 years), with our youngest patient diagnosed at 19 years of age. This is comparable with the median age of 37 years reported by others [103].

In our study fundoplication surgery – representing patients with a history of severe GER – appeared to be the only significant predictor for BE. A high percentage of fundoplication failure after EA repair and children outgrowing their fundoplication may explain the recurrence of GER in these patients [104, 105].

We also evaluated possible determinants for esophageal metaplasia (both GM and IM) as BE is thought to evolve from GM and diagnosis of BE can be limited by sampling error (mosaic pattern of GM and IM) [106]. None of the factors were significant. In contrast, a study in 101 EA patients found the following risk factors for esophageal metaplasia (GM and IM): long gap EA, age >30 years, recurrent TEF, esophageal stricture resection during childhood, esophageal stricture in adulthood, and abnormal esophageal manometry [107]. However, in half of the patients diagnosed with metaplasia no columnar-lined esophagus was observed at endoscopy. The same discrepancy between histological evidence of metaplasia and suspected BE (columnar-lined esophagus) at endoscopy was present in another study [108]. It seems that biopsies were taken from the cardia instead of the (absent) metaplastic columnar epithelium in the esophagus, which highlights the importance of accurate recognition of endoscopic anatomical landmarks in the diagnosis of BE [109]. If done not correctly, it may lead to inaccurate prevalence data of BE in EA patients.

Esophageal cancer

Esophageal cancer is the 8th most common cancer worldwide, with an incidence in developed countries of 6.4 (♂) and 1.2 (♀) per 100,000 [110]. The two commonest types of esophageal cancer are EAC deriving from the columnar mucosa and esophageal squamous cell carcinoma (ESCC) originating from the squamous mucosa.

Over the last decades, survival of EA patients has increased and many more patients reach adulthood. To date – together with the cases reported in Chapter 7 – 11 cases of esophageal carcinoma in adult EA patients have been reported at an alarmingly young age: three EAC and eight ESCC [37, 111-115]. The youngest was nearly 20 years old [113].

As above mentioned BE is a premalignant lesion which predisposes to EAC. In the general population GER, use of tobacco, obesity, and hiatal hernia are the major risk factors for EAC [102]. ESCC has several other risk factors such as low socioeconomic status, tobacco smoking, alcohol consumption, dietary factors, achalasia, and human papilloma virus [102, 116].

However, ESCC – which is not directly related to reflux – is seen more often than EAC in EA patients. In our screening and surveillance program described in Chapter 6 we found ESCC in 0.7% of EA patients, which is 108-fold higher compared to the general population.

The relatively young age at time of cancer diagnosis, the presence of only a few carcinogenic factors and the high cancer incidence in EA patients suggests an increased risk for carcinogenesis after EA repair. The reason for a possible higher prevalence of ESCC compared to EAC in EA patients is still unknown. EA patients could be at higher risk of developing ESCC than EAC. Or the time needed for EAC to evolve from BE could be longer than our median follow-up time (25.4 years).

In achalasia patients esophageal stasis of food and fluids – causing bacterial overgrowth with nitrosamine production – is thought to increase the risk to develop ESCC [117, 118]. The same pathogenesis might explain ESCC development in EA patients. As most ESCC had developed at or near the anastomosis (mid-distal esophagus), several authors have suggested that frequent dilation procedures with associated mucosal tears, scarring and inflammation predispose for ESCC [111, 112]. Prospective data from multicenter collaborative initiatives are needed to further evaluate carcinogenesis in EA patients.

Screening and surveilllance programs

Detecting potential pathological lesions at the earliest possible stage can perhaps prevent mortality from esophageal carcinoma at a young age, which is why endoscopic surveillance of EA patients at a young age is currently advocated [4]. Yet the ideal follow-up schedule has to be determined. It is important to identify patients who are at risk for carcinogenesis and will need the most intensive surveillance.

As it is still unclear which EA patients are at risk for esophageal cancer development, we started screening all EA patients in our center from the age of 17 years onwards. Our proposed surveillance intervals for BE are in accordance with the ACG guidelines [97]. In addition, in the absence of BE surveillance intervals of 5 years (age <30 years) or 3 years (age ≥30 years) are advised FIGURE 8.2.

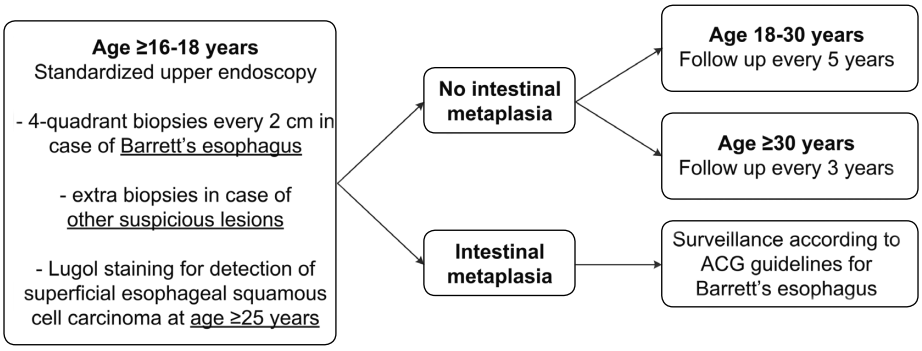

Figure 8.2 Flowchart of screening and surveillance program in adult esophageal atresia patients.

We recommend to perform chromoendoscopy with Lugol's staining from the age of 25 years onwards to examine the squamous epithelium in detail [119]. As most ESCC were found near or at the anastomosis one could consider to take random biopsies mid-esophageal at the site of the original TEF or anastomosis. Further long-term prospective cohort studies are needed before a more evidence based cost-effective surveillance program in EA patients can be implemented.

Since EA is a rare disease and only a few clinicians are involved in medical care for EA patients, a minority of clinicians are aware of the increased risk for carcinogenesis after EA repair. Moreover, since most EA patients do not experience dysphagia or GER related symptoms as troublesome, only a small percentage of adult EA patients visit their general practitioner. This illustrates the need for more awareness among general practitioners, for multicenter collaboration and for initiation of national surveillance programs.

CONCLUSIONS

In conclusion, there is a high need for multicenter research to optimize long-term gastrointestinal follow-up of EA patients. Since EA is a rare condition, multicenter collaborative initiatives (international and national) are essential, preferably randomized trials. Standardized treatment protocols and uniform definitions to report clinical parameters are essential to compare different patient cohorts. Consensus meetings are needed to achieve consensus on and formulate recommendations for the care of EA patients. Hence, the International Network on Esophageal Atresia (INoEA) was formed in 2013 to help formulate clinical practice guidelines for the care of these patients [4]. Family support groups from all over the world are united in the European federation of Esophageal Atresia and Tracheoesophageal fistula support groups (EAT). EAT focusses on sharing knowledge, experience and resources to improve management of EA and promotes scientific research and awareness of EA. They collaborate with the medical community through organizations such as INoEA.

In 2016 the Dutch Consortium of Esophageal Atresia (DCEA) was established, with members from all six university hospitals involved in neonatal surgery in the Netherlands and board members of the active Dutch patient support group 'Vereniging voor Ouderen en Kinderen met een Slokdarmafsluiting' (VOKS). In this thesis, we have shown the first publication of the DCEA study group involving 5/6 university hospitals (Chapter 5).

Since 2016 the European Commission installed 25 European Reference networks for 7,000 rare diseases. The European Reference Network on rare intestinal, Inherited and Congenital Anomalies (ERNICA) is a multidisciplinary network of highly specialized healthcare professionals focusing on congenital gastrointestinal diseases such as EA and several acquired

gastrointestinal diseases [120]. For EA, both patient support groups and medical centers are represented at international level in the workstream of diseases of the esophagus, which allows establishment of international protocols and definitions.

Structural follow-up of all children with EA should be considered up to adulthood, since it is unknown whether growth remains normal during puberty. Dieticians, as part of a multidisciplinary team, should be involved during (initial) hospitalization and follow-up to optimize nutritional status in early years, which is crucial for normal brain and immune system development.

Transition of adolescents from pediatric care to adult Gastroenterology departments is important to provide life-long endoscopic follow up to facilitate early diagnosis of relevant esophageal lesions. Since fundoplication surgery is a risk factor for both growth impairment and BE, structural follow-up in both child- and adulthood seems particularly important in this group of patients. Risk stratification in patients with EA is important to define which subgroup of patients should receive endoscopic follow-up and at which frequency. Development of a predictive score, incorporating clinical, endoscopic, biochemical and genetic factors, is required to risk stratify patients with EA. This would allow focusing of surveillance endoscopy on patients deemed to be at a higher risk of progression to esophageal cancer, making this strategy more cost-effective.

Genetic studies may serve to develop optimal risk stratification for carcinogenesis in EA patients and contribute to development of an evidence-based surveillance program from birth into adulthood. We hypothesize that chronic GER resulting in BE is not the only risk factor for esophageal carcinogenesis in EA patients as ESCC – which has an etiology unrelated to GER – is more often reported in EA patients than EAC. We believe the following genetic studies are needed:

- Whole genome sequencing to identify somatic gene mutations in EA patients who developed BE/EAC or ESCC and evaluate whether they differ from control patients without EA.
- Targeted sequencing to evaluate germline variants (single nucleotide polymorphisms; SNPs) near genes that are important for both foregut development and development of BE/EAC or ESCC – *FOXF1*, *BARX1*, *FOXP1*, *TBX5*, *GDF7* genes – in EA patients.

In 2016, we started to prospectively collect esophageal biopsies and blood samples of adult EA patients in a Biobank. In the future, these materials can be used to search for predictors of malignant progression in EA patients.

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9

Summary
Nederlandse samenvatting

SUMMARY

This thesis aimed to optimize long-term gastrointestinal follow-up of esophageal atresia (EA) patients. In this chapter, the main findings and conclusions of our studies will be summarized.

Since gastrointestinal problems can compromise growth, Chapter 2 describes longitudinal evaluation of growth in 126 EA patients from infancy up to school age. Compared with the general population, EA patients had a significantly lower weight up to five years of age. A significantly lower height was found in the first eight years of life. Both weight and height had normalized, however, at 12 years of age. Two of the studied explanatory variables – low birth weight and a history of fundoplication surgery – were associated with lower standard deviation scores for both height and weight.

Chapter 3 provides an overview of the current knowledge regarding long-term gastrointestinal morbidity after EA repair. Nowadays survival after EA repair is approaching 100% in dedicated centers. In almost all EA patients esophageal motility is disturbed and gastroesophageal reflux (GER) is prevalent in both children and adults. GER results in gastrointestinal problems such as dysphagia, esophageal strictures, esophagitis, Barrett's esophagus (BE), and esophageal cancer. Structured follow-up programs run by multidisciplinary teams may help to reduce morbidity in EA patients. Guidelines on esophageal follow-up in EA patients were missing at time of writing this chapter. The few strategies for esophageal surveillance programs suggested in literature are shortly mentioned.

The results of routine evaluation of GER in EA patients aged ≤18 months and 8-years old using combined pH and impedance monitoring are evaluated in Chapter 4. Both infants and school-aged children experience non-acid refluxes more frequently than acid refluxes. After manual revision of the tracings a high percentage of reflux events was deleted. This raises the question whether automated analysis is accurate enough to identify impedance reflux patterns in patients with complex motility disorders such as EA.

Chapter 5 describes the incidence of refractory strictures of the esophageal anastomosis in a large national multicenter cohort of 454 children born with EA. Determinants of refractory stricture formation (isolated EA, anastomotic leakage and the need for esophageal dilation within 28 days after EA repair) are discussed in more detail in this chapter.

In Chapter 6 we describe the first results of a screening and surveillance program in EA patients. Since 2013, all adult EA patients (≥17 years) have been referred to the Gastroenterology department of our center for endoscopic screening and surveillance of (pre)malignant esophageal lesions. Endoscopic and histological results from 151 participants were included.

In 6.6% the premalignant lesion BE was present, which is 4-5 fold higher compared to the general population. Of the studied explanatory variables only a history of fundoplication surgery was associated with BE. Esophageal squamous cell carcinoma (ESCC) developed in 0.7%, which was 108-fold higher compared to the general population. Recent guidelines (2016) recommend surveillance endoscopy in EA patients, however the ideal surveillance strategy has yet to be determined.

Chapter 7 describes four EA patients who developed a gastrointestinal cancer at a relatively young age. Three patients developed an esophageal carcinoma and one patient developed a colorectal carcinoma in a colonic interposition. The relatively young age at time of cancer diagnosis, the presence of only a few carcinogenic factors and the high cancer incidence in EA patients suggests an increased risk for carcinogenesis after EA repair.

The general discussion in Chapter 8 addresses the research described in this thesis in connection with the literature, describes the strengths and limitations of the studies presented in this thesis and highlights directions for further research. The major recommendations are the following:

- Structural follow-up of all children with EA – especially those who underwent fundoplication surgery – should be considered up to adulthood, since it is unknown whether growth remains normal during puberty. Dietitians, as part of a multidisciplinary team, should be involved during (initial) hospitalization and follow-up to optimize nutritional status in early years, which is crucial for normal brain and immune system development.
- A large overdetection of retrograde bolus movements is present in automated analysis of pH and impedance measurements in EA patients, which emphasizes the need for refinement of automated software for the use in infants and children with EA. The high number of non-acid retrograde bolus events with a normal reflux index (acid index) in infants and children with EA questions the need for standard anti-acid therapy in these patients.
- To further elucidate the mechanisms involved in refractory anastomotic stricture formation, studies focusing on different surgical techniques should be performed. Research with pH and impedance monitoring and/or esophageal biopsies (histological esophagitis) could investigate the role of GER in refractory stricture formation.
- Transition of adolescents from pediatric care to adult Gastroenterology departments is important to receive life-long endoscopic follow up to facilitate early diagnosis of relevant esophageal lesions. Since fundoplication surgery is a risk factor for both growth impairment and BE, structural follow-up in both child- and adulthood seems particularly important in this group of patients.
- Multicenter collaboration, the use of uniform definitions to report clinical parameters (e.g. esophageal gap length, GER, esophageal strictures) and longitudinal data collection is needed to answer the question 'How to optimize gastrointestinal long-term follow-up in EA patients?'.
- Collecting esophageal biopsies and blood samples in a Biobank is needed to search for predictors of malignant progression in EA patients.

NEDERLANDSE SAMENVATTING

Dit proefschrift richt zich op het optimaliseren van de lange termijn zorg voor maagdarmproblemen bij patiënten geboren met een slokdarmatresie. In dit hoofdstuk worden de belangrijkste bevindingen en conclusies van onze studies samengevat en besproken. Verder zullen suggesties voor toekomstig onderzoek worden gepresenteerd.

Slokdarmatresie (oesofagusatresie) is een relatief veelvoorkomende aangeboren afwijking (congenitale aandoening / geboortedefect) waarbij de slokdarm (oesofagus) en luchtpijp (trachea) betrokken zijn. Het is de meest voorkomende aangeboren afwijking van de slokdarm. In Europa is één op de 4.000 pasgeborenen geboren met een slokdarmatresie. In Nederland worden er jaarlijks 35-55 kinderen geboren met slokdarmatresie (1 per 4.000 geboortes).

Atresie is de term die gebruikt wordt om een aangeboren afwijking te beschrijven waarbij een natuurlijke lichaamsopening afgesloten is of geheel ontbreekt. In kinderen geboren met slokdarmatresie is het middelste gedeelte van de slokdarm afwezig en niet verbonden met het onderste gedeelte van de slokdarm, welke verbonden is met de maag. Een kind geboren met slokdarmatresie heeft last van teruggeven van voeding en speeksel doordat dit niet naar de maag kan passeren. Kinderen geboren met een slokdarmatresie hebben vaak ook een verbinding tussen de slokdarm en luchtpijp, een zogeheten tracheo-oesofageale fistel. Deze fistel – afhankelijk van de precieze locatie in de slokdarm – zorgt ervoor dat voeding, speeksel en maagzuur in de luchtpijp en longen terecht komt. Als de tracheo-oesofageale fistel niet snel na geboorte opgespoord en behandeld wordt, kan het pasgeboren kind ademhalingsproblemen, een luchtweginfectie (longontsteking) of zelfs een acute obstructie van de bovenste luchtwegen met een daaropvolgende acute ademstop ontwikkelen.

Een kind kan geboren worden met een geïsoleerde slokdarmatresie, een geïsoleerde tracheo-oesofageale fistel of een combinatie van de twee (meest voorkomend). Via het classificatiesysteem van Gross wordt slokdarmatresie onderverdeeld in vijf types: type A (geïsoleerde slokdarmatresie), type B (slokdarmatresie met fistel hoog in de slokdarm), type C (slokdarmatresie met fistel laag in de slokdarm), type D (slokdarmatresie met twee fistels) en type E (geïsoleerde tracheo-oesofageale fistel) FIGUUR 1.1.

Aangezien maagdarmproblemen de groei negatief kunnen beïnvloeden beschrijft Hoofdstuk 2 de groei van geboorte tot aan de schoolleeftijd van 12 jaar in 126 kinderen met slokdarmatresie. In vergelijking met de algemene populatie hadden kinderen met slokdarmatresie een significant lager gewicht tot aan de leeftijd van vijf jaar. Een significant kleinere lengte werd in de eerste acht levensjaren gezien. Zowel gewicht als lengte waren bij 12 jaar genormaliseerd. Twee van de bestudeerde potentieel verklarende variabelen – laag geboortegewicht en

anti-reflux chirurgie (operatie tegen het omhoogkomen van maagzuur in de slokdarm) – waren geassocieerd met het achterblijven van gewicht en lengte.

Hoofdstuk 3 beschrijft de huidige kennis over maagdarmproblemen die op de lange termijn ontstaan na operatief herstel van een slokdarmatresie. De overleving na een herstel-operatie nadert 100% in gespecialiseerde centra. In bijna alle slokdarmatresiepatiënten zijn de ritmische bewegingen van de slokdarm – bijvoorbeeld tijdens het slikken – verstoord en komt omhoogkomend maagzuur (reflux) veel voor bij zowel kinderen als volwassenen. Reflux zorgt voor maagdarmproblemen zoals slikklachten, vernauwingen van de slokdarm, slokdarmontsteking, Barrettslokdarm en slokdarmkanker. Bij een Barrettslokdarm is het slijmvlies in de slokdarm veranderd, waarbij er een verhoogde kans is op het ontstaan van slokdarmkanker. Gestructureerde follow-up programma's met multidisciplinaire teams kunnen de problemen bij slokdarmatresiepatiënten mogelijk verminderen. Ten tijden van het schrijven van dit hoofdstuk ontbraken richtlijnen voor periodieke controle van de slokdarm in slokdarmatresiepatiënten. De paar strategieën voor slokdarm surveillance programma's die in de literatuur beschreven zijn worden kort genoemd.

In Hoofdstuk 4 worden de resultaten van pH-impedantie metingen bij kinderen van ≤18 maanden en 8 jaar oud beschreven. Bij zowel de baby's als bij de oudere kinderen kwam niet-zure reflux vaker voor dan zure reflux. Na handmatige revisie van de metingen werd een hoog percentage refluxmomenten verwijderd. Het is dus de vraag of automatische analyse van deze metingen accuraat genoeg is om refluxpatronen te kunnen identificeren bij patiënten met complexe motiliteitsstoornissen zoals slokdarmatresie.

Hoofdstuk 5 beschrijft de resultaten van een grote nationale multicenterstudie in 454 kinderen met slokdarmatresie, waarin het ontstaan van hardnekkige terugkerende slokdarm-vernauwingen werd onderzocht. Risicofactoren voor het krijgen van een hardnekkige terugkerende slokdarmvernauwing zijn: een slokdarmatresie zonder fistel (Gross type A), naadlekkage na de slokdarmoperatie en een slokdarmvernauwing binnen 28 dagen na de slokdarmoperatie.

Om (kwaadaardige) afwijkingen van het slokdarmslijmvlies tijdig op te sporen wordt in recente richtlijnen (2016) aangeraden om de slokdarm van volwassenen geboren met een slokdarmatresie regelmatig te controleren, echter moet de ideale surveillancestrategie nog bepaald worden. Het Erasmus MC is sinds 2013 gestart met een screening en surveillance programma, waarbij patiënten vanaf 17 jaar oud bij de MDL-arts op de polikliniek gezien worden. Na overleg wordt er middels een kijkonderzoek in de slokdarm (gastroscopie) het slokdarmslijmvlies beoordeeld. De resultaten hiervan worden beschreven in Hoofdstuk 6 . Van de 151 patiënten werd er in 6,6% Barrettslokdarm gevonden, dit is 4-5 keer hoger dan te verwachten is in de algemene populatie. Van de bestudeerde potentiele verklarende

variabelen was enkel anti-reflux chirurgie geassocieerd met het ontwikkelen van Barrett-slokdarm. Van alle patiënten ontwikkelde 0,7% slokdarmkanker (plaveiselcelcarcinoom), wat 108-maal hoger is dan in de algemene populatie te verwachten valt.

In Hoofdstuk 7 worden vier slokdarmatresiepatiënten beschreven die op jonge leeftijd kanker van het bovenste deel van het maagdarmkanaal hebben ontwikkeld. Drie patiënten kregen slokdarmkanker en een patiënt kreeg dikke darmkanker in een stuk dikke darm wat op kinderleeftijd gebruikt was om de slokdarm met de maag te verbinden (colon-interpositie). De relatief jonge leeftijd waarop de kanker werd gevonden, de aanwezigheid van maar een paar bekende risicofactoren voor kanker en de hoge kankerincidentie bij slokdarmatresie-patiënten suggereert een verhoogd risico op ontstaan van kanker na herstellen van slokdarmatresie.

De algemene discussie in Hoofdstuk 8 behandelt de volgende punten: de onderzoeken uit dit proefschrift in relatie tot de literatuur, de sterke en zwakke punten van de onderzoeken uit dit proefschrift en de richtingen voor toekomstig onderzoek. De belangrijkste aanbevelingen zijn de volgende:

- Structurele follow-up van alle kinderen met slokdarmatresie – in het bijzonder diegene die een anti-reflux operatie hebben gehad – dient tot de volwassen leeftijd overwogen te worden, aangezien het onbekend is of groeiontwikkeling normaal blijft tijdens de pubertijd. Diëtisten, als onderdeel van een multidisciplinair team, dienen betrokken te zijn tijdens (initiële) ziekenhuisopname en follow-up om de voedingsstatus in de vroege jaren te optimaliseren, wat cruciaal is voor normale ontwikkeling van hersenen en immuunsysteem.
- Met automatische analyse van pH-impedantie metingen in slokdarmatresiepatiënten vindt overdetectie van reflux plaats. Dit laat de noodzaak zien voor het verfijnen van automatische software voor het gebruik bij kinderen met slokdarmatresie. Het hoge aantal niet zure refluxmomenten bij een normale refluxindex (zuurindex) bij kinderen met slokdarmatresie stelt de noodzaak voor standaardbehandeling met zuurremmers in deze patiënten ter discussie.
- Studies die zich focussen op verschillende operatietechnieken voor herstellen van slokdarmatresie zijn nodig om het mechanisme achter het ontwikkelen van een hardnekkige terugkerende slokdarmvernauwing verder te bekijken. Onderzoeken met pH-impedantie metingen en/of slokdarmbiopten (histologische oesofagitis) kunnen de rol van reflux bij het ontstaan van hardnekkige terugkerende slokdarmvernauwing onderzoeken.
- Overgang van Kindergeneeskunde naar de volwassen Maag-darm-leverziekten afdeling is belangrijk voor levenslange endoscopische follow-up om relevante slokdarmafwijkingen in een vroeg stadium op te sporen. Aangezien anti-reflux chirurgie een risicofactor voor zowel groeiachterstand als Barrettslokdarm is, lijkt structurele follow-up in zowel kinderen als volwassenen belangrijk in deze specifieke groep patiënten.

- Samenwerking tussen verschillende centra, het gebruik van uniforme definities voor het vastleggen van klinische parameters (bijv. lengte slokdarmatresie, reflux, slokdarmvernauwingen) en longitudinale dataverzameling is noodzakelijk voor het beantwoorden van de vraag 'Hoe optimaliseer je de lange termijn zorg voor maagdarmproblemen bij patiënten geboren met een slokdarmatresie?'.
- Om naar voorspellers van kwaadaardige progressie bij patiënten geboren met een slokdarmatresie te zoeken is verzameling van slokdarmbiopten en bloedmonsters in een biobank nodig.

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

Acronyms

CHARGE	coloboma, heart defects, atresia of the choanae, retardation of growth, genital and urinary abnormalities, ear abnormalities and/or hearing loss
VACTERL	vertebral anomalies, anal atresia, cardiac anomalies, tracheoesophageal fistula, renal anomalies, and limb defects

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Co-promotors	Prof. dr. M.C.W. Spaander
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General academic skills	**Year**	**Workload**
Research Management for PhD's	2014	1.0 ECTS
Endnote + systematic literature research Pubmed and other databases	2014	1.0 ECTS
Introduction Course on SPSS	2015	1.0 ECTS
Introduction in Graphpad Prism	2015	0.3 ECTS
Biomedical English Writing Course	2015	2.0 ECTS
Poster presenting workshop	2015	0.1 ECTS
Research Integrity	2015	0.3 ECTS
BROK	2016	1.0 ECTS
CPO-course 'Patient Oriented Research: design, conduct and analysis'	2016	0.3 ECTS
Open Clinica Course	2016	0.3 ECTS
Workshop Indesign CS6	2016	0.3 ECTS
Workshop Microsoft Access 2010: Basic and advanced	2016	0.6 ECTS

Research skills	**Year**	**Workload**
Web-seminar Pediatric Impedance-pH monitoring	2015	0.1 ECTS
SNP Course XII: SNPs and Human Diseases	2015	2.0 ECTS

Teaching skills	**Year**	**Workload**
BKO training coaching bachelor students	2016	0.2 ECTS
BKO intervision group meetings	2016	0.1 ECTS

Teaching activities	**Year**	**Workload**
Coach of 10 bachelor medical students	2016-2017	1.4 ECTS

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6th Lagerhuisdebat Hepatitis B and C, Utrecht, The Netherlands	2014	0.1 ECTS
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Diner Pensant Hepatologie, Rotterdam, The Netherlands	2015	0.1 ECTS
Echocursus Dutch Liver Week, Amsterdam, The Netherlands	2015	0.2 ECTS
PhD day Gastroenterology and Hepatology, Rotterdam, The Netherlands	2015	0.2 ECTS
Sophia Research Day, Rotterdam, The Netherlands	2015	0.2 ECTS
PhD day Gastroenterology and Hepatology, Rotterdam, The Netherlands	2016	0.2 ECTS
31th Erasmus Liver day, Rotterdam, The Netherlands	2016	0.2 ECTS
Sophia Research Day, Rotterdam, The Netherlands	2017	0.2 ECTS

Attended (inter)national conferences	Year	Workload
3rd International Conference on Esophageal Atresia, Rotterdam, The Netherlands	2014	0.6 ECTS
Twice annual meeting of the Netherlands association of Gastroenterology and Hepatology, Veldhoven, The Netherlands	2014	0.6 ECTS
10th GE Jaarsymposium, Rotterdam, The Netherlands	2015	0.3 ECTS
Twice annual meeting of the Netherlands association of Gastroenterology and Hepatology, Veldhoven, The Netherlands	2015	0.6 ECTS
15th Annual Congress of the European Paediatric Surgeons' Association (EUPSA), Ljubljana, Slovenia	2015	1.0 ECTS
23th United European Gastroenterology Week (UEGW), Barcelona, Spain	2015	1.0 ECTS
11th GE Jaarsymposium, Amsterdam, The Netherlands	2016	0.3 ECTS
4th International Conference on Esophageal Atresia, Sydney, Australia	2016	1.0 ECTS

Oral presentations	Year	Workload
High prevalence of Barrett's esophagus and histological inflammatory changes in patients after esophageal atresia repair. Twice annual meeting of the Netherlands association of Gastroenterology and Hepatology, Veldhoven, The Netherlands	2015	1.0 ECTS
High prevalence of Barrett's esophagus and histological inflammatory changes in patients after esophageal atresia repair. 15th Annual Congress of the European Paediatric Surgeons' Association (EUPSA), Ljubljana, Slovenia	2015	1.0 ECTS
High prevalence of Barrett's esophagus and histological esophagitis after esophageal atresia repair. Sophia Research Day, Rotterdam, The Netherlands	2015	1.0 ECTS
High prevalence of Barrett's esophagus, esophagitis and esophageal cancer after esophageal atresia repair: an update. 4th International Conference on Esophageal Atresia, Sydney, Australia	2016	1.0 ECTS

Poster presentations	Year	Workload
High prevalence of Barrett's esophagus and histological esophagitis after esophageal atresia repair. 23th United European Gastroenterology Week (UEGW), Barcelona, Spain	2015	0.5 ECTS
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ABOUT THE AUTHOR (CURRICULUM VITAE)

Florence Wilhelmina Theresia (Floor) Vergouwe was born on January 17th 1988 in Amsterdam, The Netherlands. She attended the Montessori Lyceum Amsterdam (MLA), where she graduated in 2006.

She started medical school at the University of Amsterdam in the same year. During the bachelor phase of medical school she conducted extra-curricular research at the department of Gastroenterology and Hepatology at the Academic Medical Center in Amsterdam. She investigated acute strength of various endoscopic colonic closure techniques in an ex vivo porcine colonic model. In 2010 she obtained her doctoral degree after completing her graduation research on mismatch repair deficiency in colorectal cancer patients in the Northern Cape, South Africa. This research was performed at the department of Surgery of the Groote Schuur Hospital in Cape Town, South Africa. After completing her internships in, among others, the University Hospital Brussels, Belgium, she obtained her qualification as a Medical Doctor with cum laude honors in 2013. Hereafter, she worked one year as a resident not in training (ANIOS) at the department of Internal Medicine of Tergooi Hospitals in Hilversum and Blaricum. In September 2014 she started her PhD research on long term gastrointestinal outcome in patients born with esophageal atresia, as described in this thesis. This research was performed at the department of Gastroenterology and Hepatology and the department of Pediatric Surgery of the Erasmus MC University Medical Center-Sophia Children's Hospital under supervision of Prof. dr. M.J. Bruno, Prof. dr. R.M.H. Wijnen, Dr. M.C.W. Spaander and Dr. H. IJsselstijn. During this period she was involved in establishing an endoscopic screening and surveillance program in adult esophageal atresia patients and started the Biobank Esophageal Atresia containing esophageal tissue and blood samples for future research purposes. Since January 2018, she started with her Internal Medicine residency at the Reinier de Graaf Gasthuis in Delft as part of the formal postgraduate training in Gastroenterology and Hepatology. Hereafter, she will continue her training in Gastroenterology and Hepatology at the Reinier de Graaf Gasthuis in Delft and the Erasmus MC University Medical Center in Rotterdam. She lives together with Mark de Weerd in Rotterdam.