CHILDREN WITH ESOPHAGEAL ATRESIA
Long term outcome

A study of the literature and a follow up of patients treated at Rikshospitalet University Hospital

Student thesis by

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Preword

My beautiful daughter Hanna was born with esophageal atresia in 1997. I did not know much about EA at that time. In the early years Hanna frequently suffered from respiratory infections and her “barking cough” was her trade mark. In 2008 Hanna was put on anti reflux medication as she developed symptoms of gastroesophageal reflux. All the time Hanna has been a healthy girl in spite of the complications. The sequela have not restricted her from playing football, the flute and attending school and leisure activities as her peers do.

Leaving the paediatrics department after successful primary repair of EA in 1997, I felt I had very little knowledge of EA. I decided to find out more, but I did not do much about it until 2004.

At that time, I was enrolled into the medical programme of Oslo University. Ever since it has always been my plan to find out more about EA patients and the sequela they may have after primary repair of EA. It ended in a student thesis on long term outcome in children with esophageal atresia.

I hope that maybe one day Hanna and my family will enjoy this thesis.

I am very grateful for the assistance of my supervisors, Anne Faugli and Ragnhild Emblem.

Abstract

Purpose

The aim of the study was to report long term outcome in esophageal atresia (EA) patients by a study of the literature. Special emphasis has been put on the potential association between esophageal atresia, gastroesophageal reflux, esophagitis and development of esophageal cancer. In addition, long term function in 21 adolescents with EA treated at Rikshospitalet University Hospital was assessed.

Methods

A Pub Med search for the period January 1988 until September 2008 was made identifying studies using the terms esophageal atresia, gastroesophageal reflux, respiratory function, scoliosis, quality of life, long term outcome and esophageal cancer. The terms were combined. 21 EA adolescents were included in a patient study. Symptoms from the respiratory and gastrointestinal tract as well as quality of life were assessed at long term follow up by a specialized nurse and a pediatric surgeon different from the surgeon operating the patients in the neonatal period.

Results

In long term follow up studies 30 % - 80 % of EA patients report symptoms from the respiratory tract, and pulmonary function is impaired in 10 % – 70% of patients. Dysphagia was reported in 30% - 60% of the patients and GER in 10% to 70% of patients. Chest wall asymmetry was reported in 25% of EA patients in one study. A majority of EA patients report a good quality of life. However increased risk for learning, emotional and behavior problems was reported in one study. Also, one study found that mental health and psychosocial functioning may be associated with declined health and esophageal dilatations. 6 cases of esophageal cancers in EA patients have been reported.

On long term follow up of 21 adolescents, 16/ 21 (76%) reported symptoms from the respiratory tract. 6/ 21 (29 %) reported symptoms of gastroesophageal reflux and dysphagia was reported by 10/21 (48 %). 7/21 (35%) were below the 25% percentile on weight by height adjustments. A majority of EA patients (16/21, 76%) have a good quality of life.

Conclusion

Respiratory tract symptoms in 76% of EA adolescents on follow up seem high compared to the reports in the literature. This may be due to a rather extensive detailed questionnaire. Prevalence of dysphagia and GER were the same in the Norwegian population as reported in the literature. Six cases of esophageal carcinomas have been identified in EA patients. In general, EA patients do not seem to have increased risk of esophageal cancer. However, more research is required to confirm this. In spite of the challenges EA patients may have in the early years, most patients enjoy a good quality of life.

Key words

Esophageal atresia – long term outcome – respiratory function – GER – esophageal cancer

1.0 Introduction

This paper is based on literature on long term outcome in patients with EA with respect to symptoms from the respiratory and the gastrointestinal tract, scoliosis and quality of life. Moreover, the potential association between gastroesophageal reflux and carcinomas of the esophagus has been explored.

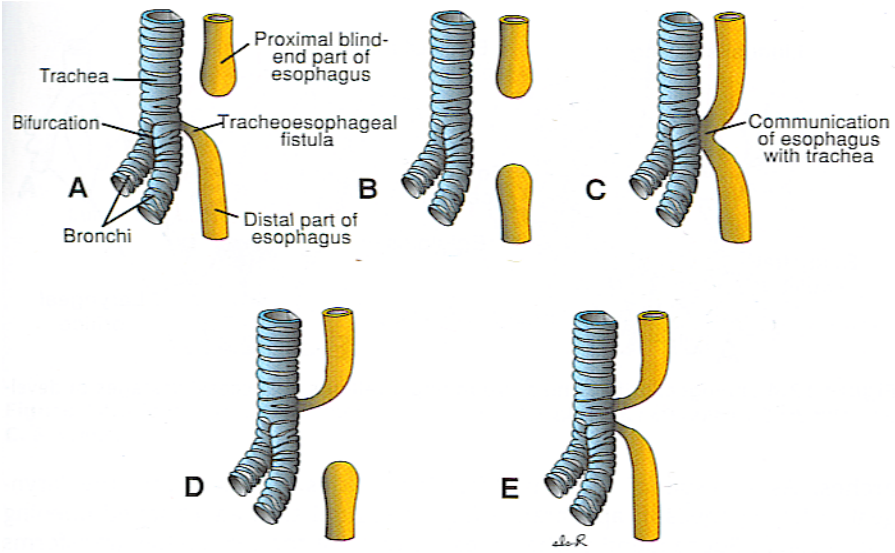
Finally, a clinical assessment of the somatic functions of 21 adolescents with EA, born 1986 through 1990, treated at Rikshospitalet University Hospital has been included. The results of the clinical assessment are, to an extent, compared to the findings in the literature study.

1.1 Esophagal atresia

Esophagal atresia (EA) is a congenital abnormality with or without tracheoesophagal fistula. In 90 % the upper portion of the esophagus is ending in a blind pouch and the lower segment forming a fistula to trachea. Of the remaining 10 %, isolated esophageal atresia and H-type tracheoesophagal fistula each make up for 4 % of incidents, whereas other variations total 2 %.

Figure 1

Types of EA
Source: Longman`s medical embryology



EA is often associated with other anomalies. Cardiac abnormalities occur in approximately 33% of cases. EA may also appear with an underlying chromosome abnormality. EA with

tracheoesophageal fistula (TEF) may also appear along with analatresia, renal anomalies and limb atresia.

Environmental risk factors may contribute to EA. An association between contact with herbicides and insecticides and EA/TEF has been found by Felix et al (2008).

1.2 Embryology

The esophagus emanates out of the lung bud (respiratory diverticulum) which appears as an outgrowth of the ventral wall of the foregut when the embryo is 4 weeks old. The lung bud is separated from the foregut by two longitudinal ridges. When these ridges fuse to form the tracheoesophageal septum, the foregut is divided into a dorsal portion, the esophagus, and a ventral portion, the trachea and lung buds.

1.3 Incidence

In the Norwegian population of the incidence of EA varies between 6 – 20 infants. In the period 1986 through 1990, as reported by the Norwegian Medical Birth Registry 69 children were born with EA.

2.0 Study of the literature

2.1 Materials and method

This study focuses on somatic function of EA children in follow up studies. A Pub Med search for the period January 1988 till September, 2008 was undertaken. Papers were identified using the terms *eosphageal atresia, gastroesophageal reflux, respiratory function, scoliosis, quality of life, follow up, long-term outcome, esophageal cancer.*

The terms were combined in the following manner (1) “esophageal atresia and respiratory function”, (2) “esophageal atresia and gastroesophageal reflux and follow up and long term outcome”, (3) “esophageal atresia and scoliosis”, (4) “esophageal atresia and quality of life”, (5) “esophageal atresia and esophageal cancer” limited to articles published during the last 10 years.

Search (1) produced 69 articles and search (2) 17 articles. Search (3) combining “scoliosis and esophageal atresia” produced 16 articles, whereas search (4) gave 10 articles. Search (5) identified 24 papers relevant for our study.

Among all these papers 38 papers were identified as relevant and included in the literature list.

2.2 Results

2.2. 1 Respiratory tract

Respiratory symptoms are common in EA/TEF patients. Respiratory symptoms reported in this literature study are in particular cough, wheeze and respiratory infections in addition to results of pulmonary function tests. Symptoms and findings of the literature study are summarized in the table below:

Table 1
Respiratory tract symptoms

Study	Yr	Subj. no	Mean age/range Years	Respiratory symptoms Subjects	Cough Subj	Respiratory Infections Subjects	Pulmonary function
Engstrand Lilja et al	2008	25	<11;15>	-	8/25 (32 %)	64% > 3 inf/year	32% with impaired exercise capacity
Malmstöm et al	2008	27	13,7 <9,7;19,4>	11/27 41% with current symptoms	7/27 (26%)	14 with pneumonia ever	FEV < 80% for 8 of 25 tested implying a restrictive pattern. FEV_1 < 87% for 7, implying an obstructive pattern. 10 of 25 normal
Taylor et al	2007	132	20 <20;48>	44/132 (33%)	5/132 (4%)	10/132 (8%)	29 (22%) with symptoms from asthma in previous 12 months
Koivusalo et al	2005	128	38 <24;54>	41/ 128 (32%)	9/128 (7%)	10/128 (13%)	33% reported poor physical performance. 14% reported shortness of breath.
Tomaselli	2003	26	15,8 <8;28>	10,5	7%	14% reported aspiration pneumonia	None of the patients reported asthma
Agrawal et al	1999	14	<7-12>	12/14 (86%)	12/14 (86%)	1 > 3 infections per year	Spirometry: Mean value for 10 observations was 2 SD below predicted FEV_1. Asthma overdiagnosed ?
Sompi et al	1998	43	12,6 <3,5:30>	9/43 (21%)	16/43 (37%) at night	9/43 (21,%) in previous year	24 underwent pulmonary function test. (PF). PF was below normal in 16 (67%). 2 responded to bronchodilator inhalation.
Ure et la	1998	50 primary repair	25,3 <20;31>	30/50 (60%)	30/50 60 %	30/50 (60%) reported frequent broncithis	15 patients (30) were short of breath some of the time.
Robertson et al	1995	25	14,8 <7;28>	-	-	11/25 (44%) had more than 3 pneumonias per year	13 of 25 had abnormal pulmonary function test (PFT). 3 obstructive (12%) with an FEV1<80%. 9(36%) restrictive 1 with a mixed pattern. 10 subjects with siblings all had better PFT
Chetcuti et al	1988	125	25 <na;39>	30/125 (24%)	11/125 (9%) daily 9/125 (8%) > 1 month	18/125 (14%) one infection per year. 12/125 (10%) > 2 infections per year.	93 patients underwent PFT. Values for FEV_1 were reduced but within the normal range. Residual lung volumes were reduced.
Biller et al	1987	12	26	5/12 (62,5%)	2/12 17%	1/12 (8%) had recurrent pneumonia in the past 10 years	Mild restrictive lung volumes reported in childhood persist well into adulthood.

2.2.2 Summary respiratory tract symtoms

Engstrand Lilja et al (2008) evaluated the sequale and outcome of 125 patients with EA treated at The University Hospital of Uppsala, Sweden in the period 1986 - 2005. Patients were divided in two groups 1986 - 1995 and 1996 - 2005 respectively. Also, in each period patients were classified in age groups 1 - 5, 6 - 10, 11 - 15, and 16 -2 0. There were 37, 33, 25 and 30 patients in the respective groups. Shortness of breath, frequent coughing, respiratory infections and impaired exercised capacity were noted in all age groups. In age group 11 -15 64 % reported more than three respiratory infections per year, 32 % reported frequent coughing, 38 % shortness of breath, 32 % impaired exercise capacity. 56 % of patients were on asthma medication.

Malmström et al (2008) characterized symptoms, pulmonary function tests and bronchial responsiveness of 27[1] adolescents after repaired esophageal atresia with TEF and correlated this with endobronchial biopsy findings. Tracheomalacia was diagnosed in 20 patients. The study found that asthma was diagnosed by doctors in 22% of patients. A restrictive and obstructive spirometric defect was observed in 41% and 44% respectively. Increased bronchial responsiveness, detected in 24% of patients, was weakly associated with current respiratory symptoms and low forced vital capacity. At the time of the clinical examination 11 of 27 patients reported current respiratory symptoms.

Taylor et al (2007) studied 132 patients corrected for EA at the Royal Children's and St Vincent's Hospital in Melbourne, Australia. Patients were invited by telephone to attend the clinic. All patients were 20 years and older. In addition to pediatric surgeons gastroenterologists attended the clinic. Clinical assessment was based on an examination and questionnaire focusing mainly on respiratory and upper GI tract symptoms in past 12 months. 44 patients had symptoms. Of these 29 patients had asthma, 6 had bronchitis and 4 had pneumonia whereas 5 patients complained of persistent cough.

Koiviso et al (2005) assessed the effect of EA repair on the respiratory tract using a 15- item questionnaire on respiratory symptoms with respect to quality of life that has been developed by pulmonologists and pediatric surgeons from The Childrens Hospital, University of Helsinki,

[1] 23 patients underwent spirometry

Finland. Respiratory symptoms were significantly more frequent among the EA group compared to the control group. Mild, moderate to severe respiratory symptoms totalled 41 of 128 patients with EA, whereas only 3 were affected among control subjects. Respiratory symptoms that occurred statistically significantly more often in EA patients included shortness of breath, frequent coughing, frequent respiratory tract infections and coupious mucus secretion in airways

Agrawal et al (1999) compared respiratory function testing in infancy and adolescence. Their study of 14 children found an abnormal respiratory function in a majority of cases. Lung volumes were found to follow a restrictive pattern with a decrease in lung volumes. Mean value for 10 observations was 2 SD below predicted FEV_1. Cough was present in a majority of patients and described as unproductive. 6 of the patients were diagnosed with wheeze of which 4 patients had asthma. One patient, with a known consolidated lung lobe, had more than 3 recurrent respiratory infections per year. In spite of multiple respiratory problems encountered in infancy, most children now have minimal restrictions on school attendance, sport and travel. Agrawal et al concluded that respiratory function testing is of limited value in medium term prognosis.

Somppi et al (1998) investigated 43 patients in the years 1963 through 1993. They reported impaired quality of life for one third of the group due to respiratory infections, dyspnea, diffuculties in swallowing and coughing at night. 16 patients complained of cough whereas 9 patients had had bronchitis or pneumonia. 67% of patients had pulmonary function tests below normal whereas 10% of patients were on asthma medications. 60% of patients had experienced some symptoms from the respiratory tract.

Chetcuti et al (1988) followed 125 patients who survived until 18 years of age 1948 through 1969. Asthma was diagnosed in 17. Tracheomalacia symptoms (harsh barking cough) was present in 50 patients (40 %). Chetcuti et al discovered that there were no differences in frequency of respiratory problems between smokers and non-smokers.

Chetcuti et al found that respiratory problems were less prevalent than they had been in early childhood. Among factors that contribute to respiratory problems after esophageal atresia repair is recurrent inhalation secondary to either abnormal oesophageal motility or gastro-

oesophageal reflux. This may have entailed increased bronchial hyperreactivity and infections in the lower respiratory tract. Chetcuti also found that all patients enjoyed a normal lifestyle.

Conclusion

30 % – 80 % of EA patients report symptoms from the respiratory tract. Problems with coughing are reported by 5 % - 60 % of patients and frequent respiratory infections are reported in 10 % - 60 %. Repeating respiratory tract infections may have an impact on pulmonary function. Pulmonary function was reported to be impaired in 10 % to 70 % of patients. Obstructive as well as restrictive lung functions were recorded in these patients.

2.3 Gastrointestinal tract

In EA patients disorganized peristaltic activity of the esophagus is expected. One study (Tomaselli et al) found uncoordinated peristaltic activity in 100 % of EA patients. Following this, dysmotility of the esophagus may give rise to symptoms from the gastrointestinal tract. The prevalence of GER in the Western population has been reported to 2 % (Deurloo et al, 2005).

In this study gastrointestinal symptoms reviewed are in particular dysphagia, symptoms of gastroesophageal reflux, abdominal pain and loose stools.

Table 2
Symptoms from the gastrointestinal tract

Study	*Yr*	*Subjects no*	*Mean age (yrs)*	*GER Subj*	*Dysphagia Subj*	*Comments*
Engstrand Lilja et al	2008	25	<11;15>	11/25 (44%)	16/25 (64%)	-
Malmström et al	2008	27	13,7 <9,7;19,4>	12/27 (44%)	8/27 (30%)	23 /27 (85%) had once had esophagitis 9 /27 (33%) had heartburn
Thambipillai et al	2007	21 of which 4 died	13,5 (2,3;27)	14/21 (66%)	-	9/21 (43%) needed fundoplication. 16/21 (76%) developed strictures
Taylor et al	2007	132	20 <20;48>	83/132 (63%)	68/132 (52%)	35/ 132 (27%) used anti reflux medication
Koivusalo et al	2005	128	38 <24;54>	50/128 (39%) Total GI	-	Mild GI symptoms in 12/128 (9,4%) and severe in 38/128 (29,7%)
Little et al	2003	69	10,5 (na)	33/69 (48%)	31/69 (45%)	19/69 (28%) were fundoplicated. 2 had Barrets esoophagitis
Tomaselli et al	2003	26	15,8 <8;28>	6/26 (16,7%)	13/26 50%	-uncoordinated peristaltic activity in all 26 patients (100%)
Somppi et al	1998	43	12,6 <3,5;30>	8 / 43 (18%)	15/43 (35%)	After primary repair abnormality in esophageal perstaltis were seen in 23/31 (75%)
Ure et al	1998	50 primary repair	25,3 <20;31>	11/50 (22%)	24/ 50 (48%) reported “hold up”	11/50 (22%) had heartburn 12/50 (24%) had diarrhea 46/ 50 (92%) had unrestricted meal capacity
Chetcuti et al	1988	125	25 <na;39>	57/125 (46%)	76/125 (61%)	One patient with a hiatus hernia and a mild esophageal stricture distinct from the anastomostic site.

Engstrand Lilja et al (2008) noted that in age group 11 - 15 years 44 % reported gastroesophageal reflux and 64 % reported dysphagia. 20 % of patient stayed on anti reflux

medication (omeprazole). The prevalence of dysphagia and GER did not differ much across age groups, but there were significant differences in terms of anti reflux medication. Only 6 % of patients in age group 16 - 20 stayed on omeprazole, whereas 30 % in age group 6- 10 used omeprazole.

In Thambipillai et al (2007) study of 26 patients treated for EA, it was discovered at the time of follow-up that 66 % developed symptomatic gastroesophageal reflux, of which 43 % needed fundoplication. None were reported having respiratory symptoms at the time of examination. Also, all children were on a normal diet and had acceptable growth parameters. Median weight was at 20^{th} percentile and the median height at 50^{th} percentile.

Taylor et al (2007) found that 83 patients (63 %) suffered from reflux, whereas 68 (52 %) had dysphagia. 35 % of patients were on anti-reflux medication.

Little et al (2003) followed 69 infants for 224 months. Mean follow-up was at 125 months (10,5 years). Dysphagia (45 %), respiratory infections (29 %), GER (48 %) and choking (10 %) along with growth delays were common symptoms during the first five years. Almost half of the children weighed less than the 25^{th} percentile the first 5 years. At the ten-year follow up a substantial improvement was noted; approximately one third of patients weighed less than the 25^{th} percentile. These problems all improved as the children grew older. Long term results prove favourably to the group despite problems associated with frequent respiratory infections, early growth retardation and esophageal motility disorders.

Somppi et al (1998) investigated 43 patients in the years 1963 through 1993. 18% had gastroesophageal reflux symptoms. The study also noted that the incidence of GER increased with age.

Chetcuti et al (1988) followed 125 patients who survived until 18 years of age from the period 1948 through 1969. The study showed no deviations in terms of weight and height distributions. However, symptoms of reflux were common. Dysphagia was a complaint by 76 patients out of 125.

Conclusion

Main symptoms from the gastrointestinal tract are GER and dysphagia. On long term follow up of EA patients, dysphagia is noted in 30% - 60% whereas GER are reported in 20% to 65% of subjects.

2.3.1 Esophagitis and Barrets Esophagus

Mucosa in the distal part of esophagus can become irritated if stomach acid frequently "backs up" into the esophagus. Over time, cells in the distal part of the esophagus may change and begin to resemble the cells that line the stomach, a condition called “Barrets esophagus”. This may be a premalignant condition.

The exact risk of a patient with Barrett's esophagus developing cancer is not known. Current estimates put the risk at 40 times higher than in subjects without Barret’s. The prevalence of Barrett’s esophagus in the US population ranges from 0,4% to 0,8% (The American Society of Thoracic Surgeons).

Deurloo et al (2005) conducted a study to determine the prevalence of Barret`s esophagus in adults with EA. 23 of 38 patients underwent esophagogastroscopy (EGS) with biopsies. As many patients with complaints of GER were willing to undergo EGS as patients without complaints of GER. Biopsies were taken from 21 patients and 20 were diagnosed with esophagitis. One patient was diagnosed with Barret’s. There was no correlation between complaints and findings at histology.

Primary aims of Taylor et al (2007) was to study the prevalence of gastroesophageal reflux symptoms, dysphagia, and endoscopic evidence of esophageal disease, particularly Barret’s metaplasia, reflux esophagitis and malignancy. Endoscopic surveillance was prior to April 2001 offered only to patients with symptoms of gastroesophageal reflux or dysphagia. After April 2001 endoscopy was offered to all patients. Results of endoscopic surveillance included previous endoscopic surveillance performed within 5 years of examination.

Of the 132 patients participating in the study, 62 patients had endoscopy performed or had already had endoscopy performed during the 5 previous years. Of these patients 43 (69%) were

labeled with macroscopic esophagitis. 30/62 (48%) had mild to moderate esophagitis. Barret`s esophagus was considered to be confirmed if intestinal metaplasia was present histologically.

Table 3
Esophagitis and Barrett's esophagus in EA patients

Summary					Esophagitis				
Study	**Year**	**Aim**	**Subj.**	**Age/ range**	**Biopsy**	**Mild**	**Moderate**	**Severe**	**Barrets**
Taylor et al	2007	Primary aims to evaluate the prevelance of esophageal symptoms and pathology; develop recommendations for follow-up	132	20 / <20;48>	62	5/62 (8%)	25/62 (40%)	6/62 (10%)	7/62 (11%)
Deurloo et al	2005	Determine prevalence of Barrets and esophagitis 10 years after	86	17/ <10;26>	40	15/40 (38%)	8/40 (20%)	7/40 (18%)	3/40 (6%)
Deurloo et al	2003	To study incidence of GERD related complications after EA correction	38	34/<20;45>	21	8/21 (38%)	8/21 (38%)	3/21 (14%)	1/21 (5%)

Mild to moderate esophagitis (Table 3), confirmed by biopsy, was diagnosed in 48 % - 76 % of EA patients. Severe esophagitis was diagnosed in 10 % - 18 % and Barret's esophagus in 5 % – 11 % of EA patients.

2.3.2 Esophageal cancers

In the general healthy population, the risk of carcinomas of the esophagus under the age of 25 is indeed very small. Only 11 cases of adenocarciomas have been reported in the literature. Hassal et al (1993) refers to 10 case reports in non EA patients, in whom patients with gastroesophageal reflux developed Barret`s esophagus under the age of 25. All patients developed adenocarcinoma of the esophagus (Table 4).

Table 4
Adenocarcinomas of the esophagus in non EA patients 25 years and younger
Reported by Hassal et al and Gangopadhyay

Author	Patient age	Sex	Other medical condition	Presentation with mass or malignant stricture	Barrets	Outcome
Al Hiloo	15	M	GER/ Nissen	Yes	No	Died
Elliott	14	M	GER/ Nissen	Yes	Yes, at diagnostic endoscopy	Died
Poleynard	25	M	GER/ Nissen	Yes	Yes, at diagnostic endoscopy	Died
Farnsworth	23	F	GER/ Nissen	Yes	Yes, on resected specimen	Died
Bright	20	M	GER/ Nissen	Yes	Yes, at diagnostic endoscopy	Died
Hoeffel	11	M	GER/ Nissen	Yes	Yes, on resected specimen	Died
Hoeffel	15	M	GER/ Nissen	Yes	Yes, on resected specimen	Died
Cheu	15	M	Severe cerbal palsy	Yes	Yes, on resected specimen	Died
Hyams	19	M	Mild cerebral palsy	Yes	Yes, at diagnostic endoscopy	Died
Gangopadhyay	8	M	no information	Yes	no information	Died
Hassal	17	M	Severe cerbal palsy	No	Yes, at diagnostic endoscopy	Alive

Gangopadhyay et al (1997) reported a boy 8 years old with a previous history of vomiting after each feeding since birth, which subsided at the age of 1 year after antireflux treatment. He presented with a mass at the middle third of the esophagus. A biopsy specimen showed an adenocarcinoma. The boy did not receive any treatment due to poor socioeconomic status and died 6 months after examination.

Esophageal cancer in EA patients

There are not many reports of carcinomas of the esophagus in EA patients in the literature. Carcinomas in this context include adenocarcinomas as well as squamous cell carcinomas. During the previous 10-year period, 4 cases were identified in the literature (PubMed search). There was an equal distribution of squamous cell and adenocarcimonas with 2 cases each. In addition one case report of an adenocarcinoma (Adzick) and one case report of a squamous cell carcinoma (La Quaglia) have been described in the literature. In total 6 EA patients are reported with esophageal cancers (Table 5). The esophageal cancers were diagnosed at the age of 20 – 46 years.

Taylor et al (2007) diagnosed 1 squamous cell carcinoma. A 44-year old patient was found to have squamous cell carcinoma in the upper esophagus. The patient presented with progressive

dysphagia. Biopsies revealed squamous cell carcinoma. Deurloo et al (2001) reported of a 38 year old patient who developed dysphagia for solid foods at the age of 38. There were no complaints of epigastric pain or heartburn. Biopsy showed a squamous cell carcinoma, which was endoscopically staged as uT3N0M0.

Pultrum et al (2005) reported a case of adenocarcinoma after primary repair of EA. The patient was 22 years old at time of diagnosis. Comorbidity was a sliding diaphragmatic hernia. Reflux was significant with pH < 4 in excess of 50% of time. .

Alfaro et al (2005) reported of a 46-year old woman who in her mid twenties experienced some dysphagia. She was then treated with several esophageal dilatations and did well until some weeks prior to admission to hospital when she presented with dysphagia to solids. There was a medical history of gastroesophageal reflux in the previous 5 years. The biopsy was labeled "T3N1M0", consistent with Barret`s esophagus with high grade dysplasia and focal carcinoma in situ. Invasive cancer could not be ruled out.

Deurloo et al (2001) reported a case of an esophageal squamaous cell carcinoma in a 38 year-old man. The carcinoma occurred near to the scar of the old anastomosis. The patient had no other apparent risk factors.

Adzick (1989) reported a case of adenocarcinoma in a 20- year-old woman who underwent surgery for primary repair of EA. La Quaglia et al (1987) reported a 44-year-old woman with a squamous cell carcinoma.

Sistonen et al (2008) studied the incidence of esophageal cancer in adult patients with repaired EA. The study compared the expected incidence of esophageal cancer in the general population with the number of cancer cases and person-years at risk in the EA-group of 272 patients. Sistonen identified 3 cases of cancer but no esophageal cancer. The study points out that it is possible to exclude long-term risk for esophageal cancer after repair of EA 500-fold higher than that of the normal population. However, the authors point out that further investigations are warranted.

Table 5
Case reports of carcinomas in EA patients
1987-2008

Summary							Presenting with			
Study	Year	Subj.	Age	Carcinoma	Location	Comorbidity	Dysphagia	Reflux	Strictures	Dillatations
Taylor et al	2007	1	44	Squamous cell carcinoma	upper esophagus	Celiac disease	+	na	na	na
Pultrum et al	2005	1	22	Adenocarcinoma	midesophageal adenocarcinoma	Sliding diaphragmatic hernia	+	pH < 4 in more than 50% of time	+	+
Alfaro et al	2003	1	46	Adenocarcinoma	midesophagus	na	+	+	+	+
Deurloo et al	2001	1	38	Squamous cell carcinoma	midesophageal lesion	na	+	+	na	na
Adzick	1989	1	20	Adenocarcinoma	centred at the gastroesophageal junction	na	+	na	na	na
La Quaglia et al	1987	1	44	Squamous cell carcinoma	na	na	+	na	na	na

2.4 Scoliosis

Scoliosis is a known complication after lateral thoracotomy. Pleural scarring has been identified as one of the causes for the curves concave toward the operated side, whereas rib resections, denervation of the serratus anterior and lattismus muscles, disturbed vascularity and spinal nerve functions were considered responsible for curves convex toward the operated side.

Westfelt et al (1991) compared the incidence of scoliosis in 61 patients older than 16 years operated on in childhood years. Postthoracotomy scoliosis was found in 30% of cases, compared with 2% in the normal population. Girls were more affected than boys. In 2 patients with esophageal atresia the scoliosis was concave toward the operated side. Studies have reported scoliosis incidence rate in esophageal atresia patients ranging from 6% to as high as 50%. Breast maldevelopment has also been observed following thoracotomy in the newborn period.

Beasley (2006) found that anterior chest wall asymmetry was evident in 59 of 232 patients with repaired EA without coexisting congenital vertebral anomalies. It was also noted that anterior wall deformity was more common in patients older than 25 years. However, new operation techniques (inter costal approach, extrapleural approach, retaining innervations of the serratus anterior muscle) may in future reduce these side effects.

2.5 Quality of life

Quality of life did not seem to differ between EA subjects and control subjects. Deurloo et al (2005) investigated 97 patients with EA and found no differences in overall physical and mental health. However, in a follow up study by Bouman et al (1999) it was found that the whole group of EA children were at increased risk for learning, emotional and behavioural problems.

Ure et al (1998) found in their study that 50 children with primary anostomosis had an unimpaired quality of life. Scoring was well in line with those of normal healthy individuals. In the 8 patient group of children with long gap atresia the study found that gastrointestinal symptoms were more frequently compared to patients with primary anostomosis. Nevertheless, the long term quality of life of patients with long gap atresia was found to be acceptable.

Faugli et al (2008) assessed mental health and psychosocial functioning of 21 adolescents born 1986 – through 1990 and compared findings to the general population. Their conclusion was that mental health and psychosocial functioning did not differ from the general population. However, the study noted that some complications, such as declined height and esophageal dilatations, may have negative influence on mental health and psychosocial functioning.

Koivusalo et al (2005) addressed 128 subjects with EA repair in Finland between 1949 and 1979. Among his observations were in terms of distribution of educational status there was no major difference between the EA patient group and a control group. Also, in grading own health, EA patients did not score statistically different from a healthy control group.

Somppi et al (1988) investigated 51 patients in the years 1963 through 1993. They reported impaired quality of life for one third of the group due to respiratory infections, dyspnea, difficulties in swallowing and coughing at night.

Table 6
Psychosocial functioning in follow up studies

Study	*Yr*	*Subjects no*	*Mean age (yrs)*	*Quality of life*
Faugli et al	2008	21	13,5 <12;17>	Mental health and psychosocial functioning did not differ from healthy comparison group. Complications to EA (dilatations and declined height) may influence mental health and psychosocial functioning
Koivusalo et al	2005	128	38 <24;54>	No difference to control group
Little et al	2003	69	10,5 (na)	Good quality of life in a majority of cases
Ludman	2003	28 (1) n = 13 (2) 2 n= 15	13 <2,22>	Patients without associated anomalies were living normal lives
Bouman et al	1999	36	10,2 <8;12>	Increased risk for learning, emotional and behaviour problems?
Somppi et al	1998	43	12,6 <3,5;30>	1/3 reported impaired quality of life due to respiratory infections
Ure et al	1998	58 50 primary anostomosis 8 colon interposition	25,3 <20;31>	Unimpaired QoL compared to healthy individuals/ Acceptable for long gap patients
Chetcuti et al	1988	125 (surv.)	25 <na;39>	2/125 attributed EA to impaired QoL

Conclusion

In spite of problems in early years, most EA children report a good quality of life. However one study noted increased risk for learning, emotional and behaviour problems. Also respiratory infections seem to influence on EA patients assessement of quality of life. Mental health and psychosocial functioning may be associated with declined height and esophageal dilatations.

3.0 A follow up of patients with EA

3.1 Introduction

Respiratory tract symptoms, dysphagia, food impaction and gastroesophageal reflux are all common symptoms in children treated for EA. Also EA children may often lag behind peers in terms of growth among others due to these factors. A clinical survey of Norwegian adolescents born with EA was carried out with the objective to assess the somatic function of the group in 12 months preceding the examination at the Rikshospitalet University Hospital.

3.2 Methods and materials

The study consisted of 34 adolescents, all born with EA in the period 1986 through 1990 treated at Rikshospitalet University Hospital, Norway. One adolescent with an incomplete medical record was excluded from the survey whereas two children were not invited to participate due to present serious medical conditions unrelated to EA.
Nine children (26%) died within 2 years after birth.

Table 7
Number of adolescents participating in the study

Total number treated at our clinic		34
Deaths	9	
Excluded due to causes not associated with EA	2	
Excluded due to missing medical report	1	12
Invited into the study		22
Turned down invitation	1	1
Adolescents participating in the study		21

3.2.1 Deaths

A majority of the children who died had serious associated anomalies such as congenital heart disease and anorectal anomalies. 7 deaths were caused by cardiac failure. One death was caused by sepsis and one death were casused by Sudden Infant Death Syndrom. In addition, a majority had birth weights below 2 500 g.

Table 8
Anomalies and birthweights in patients who did not survive repair of EA
Two were excluded because of incomplete records

			Associated anomalies		
Weight	n = 7	Premature	Congenital heart defects	UTI	Other
< 1500 g	1	1	1		
> 1 500 g	6	4	4	1	2

In the group "Other", 2 patients were diagnosed with Down's syndrom.

3.2.2 Description of adolescents

Mean birth weight of patients was 2 513 g (range 1 000 – 3 340). Gestational age of the premature children ranged from 31 to 36 weeks whereas the mean was 34,5 weeks. Median duration of first hospital admittance was 28 days (range 12 – 154 days). Median age at follow up was 13 years whereas ages ranged from 12 to 17 years. There were 12 boys and 9 girls in the survey. 6 patients had serious associated anomalies. 7 (35 %) patients had weight adjusted for height below the 25% percentile[2]. 7 (33 %) patients were living with single biological parent. All patients were living with mother.

3.2.3 Procedures

The EA adolescents and one or both parents visited the hospital for follow up assessment. A pediatric surgeon different from the surgeon operating the patients in the neonatal period and a specialized nurse performed the physical examination and assessments.

[2] One patient diagnosed with coeliaki was excluded

3.3 Assessment of symptoms

A questionnaire focused on respiratory, gastrointestinal and urinary tract symptoms. Respiratory symptoms included cough, wheezing, short of breath in relation to meals and periods of bronchitis. Patients graded the complaints on cough such as daily cough, nocturnal cough and cough during meals.

Patients were asked about symptoms from the gastrointestinal tract with particular emphasis on dysphagia and food impaction, eating habits, time spent on meals, symptoms of gastroesophageal reflux and episodes with loose stools. Loose stools were defined as episodes with diarrhea.

On dysphagia, the adolescent ranged symptoms from “no”, “occasionally” and more than one episode per week. With respect to questions on meals, the adolescents were asked how much time they spent on meals, and if they avoided particular food or meals in specific social settings, for instance dinner parties. Frequency of symptoms on GER ranged from “no”, “occasionally” and “more than one episode per week”. Symptoms were described as heart burn and chest pain. In addition, they were asked if they had had any medical treatment of the reflux.

The questionnaire also included urinary tract symptoms with focus on how many, if any, urinary tract infections they have had in past 12 months and age at continence.

Weight, height and appearance of thorax were measured. Patients were assessed by asking whether or not, their esophageal atresia inhibited their social life, in terms of daily activities at school, their leisure activities or with friends.

Finally, parents were asked about general satisfaction with follow up of controls with the surgeons, the pediatric clinic nurse and the local general practitioner.

3.4 Ethics

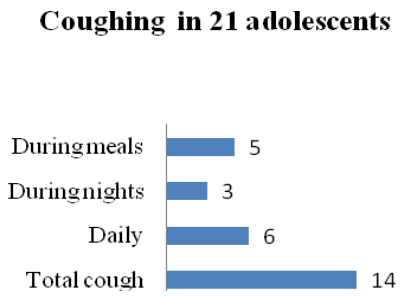
Written consent was obtained from the adolescents and parents. The study was approved by the Regional Ethics Committee for Medical Research

3.5 Results

3.5.1 Respiratory tract symptoms

Of 21 adolescents 16 (76 %) had symptoms from the respiratory tract. Most common symptoms were cough and dyspnoea combined with wheezing. 14 patients (67%) reported cough. 6 patients reported daily cough, 3 during nights and 5 during meals.

Figure 1
Coughing in 21 adolescents



13 (62 %) patients reported wheezing and dyspnea. 5 (24 %) patients had bronchitis during the preceeding 12 months. Of the latter, 3 patients had had more than one bronchitis. Most adolescents had absences from school due to infections in the respiratory tract. Days absent from school ranged from no days to 48 days with a mean of 8 days.

3.5.2 Gastrointestinal symptoms

Of the group with dysphagia, 2 (10%) were reported to experience dysphagia daily. The majority of the group with dysphagia 8/10 (80%) reported dysphagia on an occasional basis. A small majority of the total population 11/ 21 (52%) was free of symptoms.

Table 9
Dysphagia in 21 adolescents

Dysphagia	N	N = 21
Dysphagia total	10	48 %
Occasionally	8	38 %
Daily	2	10 %

5 adolescents reported that they avoided particular type of food. Vegetables, meat and white bread were most common. In terms of time spent at meals, one reported spending 45 minutes

on each meal. Adjusting for this observation, the upper range narrowed to 30 minutes. More than half of the adolescent group (11, 55%), reported that they spent more time on meals compared to peers (friends).

Table 10
Time spent on meals (minutes

Meals	N	Mean	Range
Breakfast	21	14	5 - 45
Lunch	19	15	5 - 45
At school	20	14	5 - 25
Dinner	21	23	15 - 45

3.5.2.1 Symptoms of gastroesophageal reflux

6 patients (6/21, 29%) had GER symptoms in total. There were no patients with symptoms more than once a week. None of the adolescents received medical treatment for GER during the past 12 months. In terms of practically adjusting to GER, 2 reported that when lying down, they needed to keep the head high in order to avoid reflux symptoms. In 3 adolescents a Nissen fundoplication was carried out. None of these patients experienced present GER.

Table 11
Adolescents with symptoms of gastroesophageal reflux

Gastroesophageal reflux		N = 21
Symptoms, total	6	29 %
Occasionally	6	29 %
More than once per week	0	0 %

3.5.2.2 Loose stools

One patient was diagnosed with coelicia and was excluded when assessing this symptom. Of the remaining 20, 13 (65 %) reported having experienced loose stools in the previous 12 month period. One patient reported dumping after meals and one patient reported an increase in loose stools after Nissen fundoplication.

3.5.3 Urinary tract symptoms

None of the 21 patients had a UTI in the preceding 12 months. 20 adolescents had become continent ("continent age"). "Continent age" ranged from 2,5 to 4,5 years.

3.5.4 Growth

Approximately one third of the adolescents (7/21, 35%) was below the 25% percentile on weight by height adjustments. There were 2 patients (2/20, 10%) below the 2,5% percentile. In terms of height by age, 40% (8/20) of the sample fell short of the 25% percentile.
Then body mass index (BMI) ranged 13,6 to 26,2 with a mean of 18.

Table 12

	Weight by height		Height by age	
Percentiles	N = 20	Pct	N=20	Pct
>75	3	15 %	3	15 %
[50-75]	4	20 %	6	30 %
[25,50>	6	30 %	3	15 %
<25	7	35 %	8	40 %

3.5.5 Thorax and other deformities

11 patients commented on the scar after surgery. Of these 5 patients (5/11, 45%) deemed the scar ugly. There were 2 patients with indications on scoliosis. 2 patients had scapula alata. The shoulder was “hanging down” on one patient. 3 patients had a reduced thorax diameter (“avflatet thorax”). One patient had surgery for assymetrical development of mamma.

3.5.7 Quality of life

The adolescents were asked if their EA put any constraints on their daily activities at school, with friends or in any other way. 5 patients (5/21, 24%) said they were influenced by EA. 2 patients reported constraints at school and 3 reported that EA influenced their social life with friends. The remainder (16/21, 76%) in general seemed to enjoy a good quality of life.

Five parents (n=21) reported they were receiving benefits (“Hjelpestønad og grunnstønad”) to cover expenses related to the management.

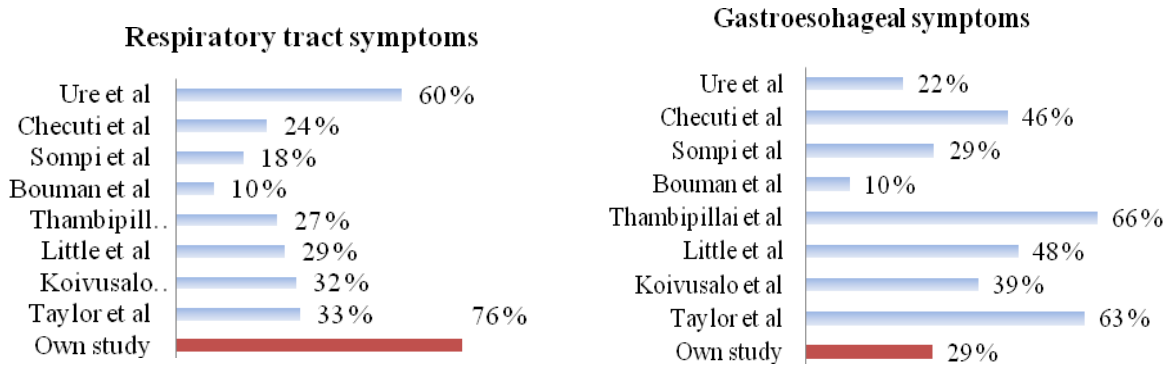
4.0 Discussion

In general, many studies of patients with EA evaluate a relatively small number of patients. The number of subjects in the literature we have studied ranged from 12 to 132 patients. Although results vary somewhat across each study, overall findings seem to be alike.

Follow up studies have focused on the major long term complications to EA. Most studies emphasize symptoms from the respiratory and gastrointestinal system. Our literature search seems to confirm what we expected prior to embarking on this study: Children born with EA report a high incidence of respiratory infections. Cough, wheezing and recurrent bronchitis have been reported in the literature and was also confirmed in our study of 21 adolescents. 16 (76%) of the group reported respiratory symptoms during the 12 months prior to the examination. The result may be higher than what we found in the literature. The higher incidence of respiratory tract symptoms in our study probably depends on an extensive questionnaire.

It is also well known that the prevalence of gastroesophageal reflux is increased in children treated for esophageal atresia. In our assessment of adolescents, we found that 6 of 21 patients (29%) had gastroesophageal reflux symptoms. 10 of 21 patients (48%) reported dysphagia. In the literature we have studied, reports on GER ranged from 22% to 66%. Reports on dysphagia ranged from 35% to 64%.

Figure 2
Literature studies and own study of adolescents



In our assessment of adolescents we found that 13 out of 20 reported loose stools. Similiar findings have not been reported in literature.

As the infant with EA grow, many of the symptoms described above seem to subside. In spite of the challenges parents and infants experience in the early years, most patients with EA seem to have a good quality of life when reaching adulthood.

Several studies have identified esophagitis as a sequale after correction of EA. Deurlo et al (2005) found esophagitis in 33 % of subjects in their study. Barrets esophagus was diagnosed in approximately 5% (7/132) of subjects in Taylor et al (2007). It is also hypothesized that Barrets esophagus is a premalignant condition to cancer. One important question to address is whether or not EA children are at a higher risk for esophageal cancer than the normal population.

The incidence of esophageal adenocarcinoma in the normal population increases with age and is very low in adolescents and young adults. In the literature 11 cases of adenocarcinomas in non EA patients below 25 years of age have been reported. Long standing gastroesophageal reflux may be linked to these cases. In EA patients 3 cases of adenocarcinomas and 3 cases of squamous cell carcinomas have been reported. The age of these patients was 22 - 46 years and was linked to gastroesophageal reflux.

It is suggested that squamous cell carcinoma can develop due to longstanding irritation and inflammation of scar tissue after frequent dilatations (Deurloo et al). The squamous cell carcinomas in EA patients reported in the literature presented at the age of 38 - 44 years.

An important question to address in this context is whether or not patients with gastroesphageal reflux and EA patients in particular should be followed up on a regular basis. It is indeed debatable whether all EA patients should be subject to endoscopic surveillance on a regular basis. Beddow et al (1999) points out that such surveillance has been advocated for adults in order to identify high risk patients prior to the development of adenocarcinoma. Lindahl et al (1995) states that all EA children should be subject to endoscopic follow up as EA children with long standing reflux have more time to develop dysplacias of the esophageal mucosa.

As gastroesophageal reflux in itself is of no benefit, it is recommended to treat it. Treatment of reflux will diminish the probability of developing dysplasia and as such comes forward as a preemptive move to avoid developing adenocarcinoma of the esophagus.

There are no authors in the literature who unanimously conclude EA children are at risk for esophageal cancer as they grow old. Following this, it may be premature to recommend long term follow up and cancer surveillance for *all* EA patients. However, for patients *at risk* follow up should be carried out and would include endoscopic surveillance on a regular basis.

As the survival rate for patients with EA have improved significantly over the past decades, more survivors now enters an age where esophageal carcinoma becomes more prevalent. Although one study has concluded that EA patients in general are not at a higher risk for incurring cancer of the esophagus than the normal population, more research is required to confirm this.

4.1 Future research

When EA children grow up, they move out from the surveillance and control of the pediatricians and pediatric surgeons. They watch them grow, but they have limited knowledge of how they adjust to their EA in adult life. Consequently, more research is required on long term results.

5.0 Literature

Author	*Title*	*Medium and date*
Adzick, S et al	Esophagal adenocarcinoma 20 years after Esophageal Atresia Repair	Journal of Pediatric Surgery, Vol 24, No 8 (August), 1989; pp 741 – 744
Agrawal, L et al	Respiratory function in childhood following repair of oesophageal atresia and tracheoeophageal fistula	ADJ.bmj.com online, 1999;81;404-408
Alfroa, L et al	Are patients who have a tracheoesophageal fistula repair during infancy at risk for esophageal adenocarcinoma during adulthood?	Journal of Pediatric Surgery (2205) 40, 719– 720
Beasley, S	Esophageal atresia: Surgical aspects	Pediatric Surgery and urology. Long term outcomes,New York: Cambridge University Press: 2006, pp 192-207
Beddow, E et al	Surveillance of Barret`s Esophagus in Children	Journal of Pediatric Surgery, Vol 34, No 1, 1999: pp 88-91
Biller, J et al	Long-term evalutaion of esophageal and pulmonary functions in patients with repaired esophageal atresia and tracheoesophageal fistula	Digestive Diseases and Sciences, Vo l32, No 9 (September 1987) pp 985-990
Bouman, N et al	Long term physical, psycological and social functioning of children with esophageal atresia	Journal of Pediatric Surgery, Vol 34, No 3 (March), 199; pp 399 - 404
Checuti, P et al	Adults who survived repair of congenital osephageal atresia and tracheo-oesophagela fistula	BMJ, volume 297, 30 July 1988 pp 344-346
Chetcuti, P	Esophageal Atresia: Nutrition, Growth and Respiratory Function,	Pediatric surgery and Urology. Long term outcomes,London: Saunders, 1998, pp 181-8
Deurloo, J	Quality of life in Adult Surviviors of Correction of Esophageal Atresia	Arch Surg/vol 140, Oct 2005, pp 976 - 980
Deurloo et al	Esophagitis and Barret esophagus after correction of esophageal atresia	Journal of Pediatric Surgery, 2005, 40, 1227-1231
Deurloo, J et al	Esophageal Squamous Cell carcinoma 38 yeras after primary repair of esophageal atresia	Journal of Pediatric Surgery, Vol 36, No 4, 2001: pp 629 - 630
Deurloo, J et al	Gastoresophageal reflux. Prevalence in adults older than 28 years after correction of esophageal atresia	Annals of Surgery, Volume 238, No 5, November 2003, pp 686-689
Engstrand Lilja, H et al	Outcome in neonates with esophageal atresia treated over the last 20 years	Pediatric Surg Int (2008) 24:531 - 536
Faugli, A et al	Mental health and psychosocial functioning in adolescents with esophageal atresia	Accepted for publication in Journal of Pediatric Surgery
Felix et al	Environmental factors in the etiology of esophageal atresia and congenital diaphragmatic hernia: Resuls of a Case-Control Study	Birth Defects Research (Part A) 82:98-105, 2008
Gangopadhyay, A et al	Correspondance: Adenocarcinoma of the esophagus in an 8 - year old boy	Journal of Pediatric Surgery, Vol 32, No 8 (August), 1997: pp 1259 - 1263
Hassall E et al	Adenocarcinoma in Childhood Barret's Esophagus: Case Documentation and the Need for Surveillance in Children	The American Journal of Gastroenterology, Vol 88, No 2, 1993,pp 282-287
Hoeffel, J et al	Esophageal adenocarcinom after gastroesophageal reflux in children	Clinical and laboratory observations, Vol 115, No 2, (1988), pp: 259 - 261
Koivusalo,A et al	Health-related quality of life in adult patients with esophageal atresia - a questionanaire study	Journal of Pediatric Surgery (2005) 40, 307 -312
Lindahl, H	Oesophageal atresia - need for life-long follow-up?	Annales Chirurgia et Gynaecologia, 1995 84:235-239
Lindahl, H et al	Chronic esophagitis and gastric metaplasia are frequent late complications of esophageal atresia	Journal of Pediatric Surgery, Vol 28, No 9 (september), 1993: pp 1178 -1180

Little, D et al	Long-term analysis of children with esophageal atresia and tracheoesophageal Fistula	Journal of Pediatric Surgery, Vol 38, No 6,(June), 2003; pp 852-856
Ludman, L et al	Quality of life after gastric transposition for oesophageal atresia	Jornal of Pediatric Surgery, Vol 38, No 1 (January), 2003: pp 53 -57
Malmström, K et al	Longitudinal follow-up of bronchial inflammation, respiratory symptoms and pulmonary function in adolsecents after repair of esophageal atresia with tracheoesophageal fistula	The Journal of Pediatrics, September 2008, pp 396-401
Norwegian Birth Registry	Birth defects: Table M1 1967-2004	http://www.fhi.no/eway/default.aspx
Pultrum, B et al	Development of an adenocarcinoma of the esophagus 22 yeras after primary repair of a congenital atresia	Journal of Pediatric Surgery (2205) 40; E1-E4
Puntis, J et al	Growth and feeding problems after repair of oesophageal atresia	Archives of Diseases in Childhood 1990, 65, 84-88
Robertson, D et al	Late pulmonary function following respair of tracheoesophageal atresia	Pediatric Pulmonology 20; 21-26 (1995)
Sadler, T	Langman`s Medical Embryology	9th edition, ISBN 0-7817-4310-9 pages 275 - 277
Sistonen, S et al	Cancer after repair of esophageal atresia: population -based long-term follow-up	Journal of Pediatric Surgery (2008), 43, 602-605
Somppi, E et al	Outcome of patients operated on for esophageal atresia;: 30 years¨s experience	Journal of Pediatric Surgery, Vol 33, No 9 (September), 1998: pp 1341 - 1346
Taylor, A et al	Gastroesophageal reflux and related pathology in adults who were born with esophageal atresia: A Long-term follow-up of esophageal atresia	Clinical gastroenterology and hepatology, 2007;5;702-706
Thambipillai, S et al	Long-term results of delayed primary anstomosis for pure oesophageal atresia: a 27 year follow up	Pediatric Surg Int (2007) 23:647 - 651
The American Society of Thoracic Surgeons		http://www.cancer.gov/cancertopics/wyntk/esophagus/page 4
Tomaselli, V et al	Long-term evaluation of esophageal function in patients treated at birth for esophageal atresia	Pediatric Surg Int (2003) 19, 40-43
Ure, B et al	Quality of life more than 20 years after repair of esophageal atresia	Journal of Pediatric Surgery Vol 33, No 3 (March), 1998: pp 511 -515
Westfelt,J et al	Thoracotomy and scoliosis	Spine:1991, Sep 16 (9);1134-1125