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Low early and late recurrence rate after open implantation of a cone-shaped patch for neonatal repair of congenital diaphragmatic hernia – a prospective cohort-study at a single referral centre with a follow-up time of two to ten years

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Wer auf etwas Gutes wartet,
wartet niemals zu lange

(Sprichwort aus Schweden)

Diese Arbeit ist all jenen gewidmet, die mit mir ‚gewartet' –
mich immer wieder freundlich erinnert, von neuem motiviert und
mit Rat und Tat unterstützt haben!

Drei Dinge helfen uns, die Mühseligkeiten des Lebens zu ertragen:
Die Hoffnung, der Schlaf und das Lachen!

(Immanuel Kant, 1724-1804)

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LIST OF ABBREVIATIONS

b	bilateral
BPD	bronchopulmonary dysplasia
CDH	congenital diaphragmatic hernia
CDH-SG	congenital diaphragmatic hernia study group
CI	confidence interval
CLD	chronic lung disease
ECMO	extracorporeal membrane oxygenation
FETO	fetoscopic endotracheal occlusion
FEV1	forced exspiratory flow at one second
FiO_2	fractional inspired oxygen
FFP	fresh-frozen plasma
FLV	fetal lung volume
GER	gastro-oesophageal reflux
HFOV	high-frequency-oscillation ventilation
iNO	inhaled nitric oxide
l (-CDH)	left-sided (congenital diaphragmatic hernia)
LHR	lung-to-head-ratio
MAP	mean airway pressure
m.d.	missing data
MIS	minimally invasive surgery
MRI	magnetic resonance imaging
NO	nitric oxide
nonR	no recurrence = no diaphragmatic complications
o/e	observed to expected
OR	odds ratio
OS	open surgery
PDA	persistent ductus arteriosus Botalli
PFO	persistent foramen ovale
PIP	peak inspiratory pressure
pO_2	partial pressure of oxygen
ppm	parts per million
PTFE	Polytetrafluorethylen
R	recurrence = diaphragmatic complications
r (-CDH)	right-sided (congenital diaphragmatic hernia)
RR	relative risk
RSV	respiratory syncytial virus
VACTERL	vertebral deformities, anal atresia, cardiac defects, tracheo-esophageal fistula, renal malformation, limb deformities
WOG	weeks of gestation

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1 INTRODUCTION

1.1 Epidemiology

Congenital diaphragmatic hernia is a rare defect, which has an incidence of 1:3000 and accounts for 8% of all congenital anomalies[1]. Since there is a hidden mortality with abortions and stillbirths not taken into account, the true incidence might even be higher[2]. Abdominal viscera prolapse into the thoracic cavity through a diaphragmatic defect, that is located on the left side in about 80% of cases and only very rarely bilateral (2%)[3]. Diaphragmatic hernia is associated with lung hypoplasia and pulmonary hypertension with consequently persistent fetal circulation. In cases of severe pulmonary hypertension right ventricular hypertrophy results – leading to relative hypoplasia of the left ventricle that can cause left ventricular failure after birth. Lung hypoplasia and pulmonary hypertension are among severe associated malformations (e.g. cardiac) the main reasons for postnatal mortality. Postnatal treatment is focusing on gentle ventilation, adequate therapy of pulmonary hypertension and delayed surgical repair after stabilization of the neonate[4]. Due to improvements in standardized prenatal diagnosis, identification of prognostic markers and standardized postnatal treatment survival-rates in specialized centres are higher than 80% and long-term morbidity is gaining more importance[5].

1.2 History

There are early reports on acquired diaphragmatic hernia, which have been described by Hippocrates, Galen, Daniel Sennert and Ambroise Paré[6]. The first case of congenital diaphragmatic hernia was reported by Lazarus Riverius in 1672: he incidentally found a right-sided diaphragmatic defect in a 24-year old man on postmortem autopsy[7].

Also, in the 1670's Isbrand van Diemerbroeck described the first affected child[8]. In 1701 Sir Charles Holt described the first infant with left-sided CDH. He also reported in detail the symptoms observed during the child's life and correlated these to his postmortem findings[9]. In London, George Macaulay presented a male neonate with left-sided CDH at the society of physicians in 1754 – and one year later he published another case of a girl with right-sided CDH. He also described the initial symptoms, noted mediastinal shift and lung hypoplasia, and

[1] Colvin et al. (2005)
[2] Wessel et al. (2015); Snoek et al. (2016b); Kardon et al. (2017)
[3] Deprest et al. (2005); Kardon et al. (2017)
[4] Reiss et al. (2010); Snoek et al. (2016)
[5] Wessel et al. (2015); Snoek et al. (2016b)
[6] Cullis and Davis (2018)
[7] Irish et al. (1996)
[8] Balfour (1869)
[9] Irish et al. (1996)

conserved both bodies, which are still displayed at the University of Glasgow (The Museum of Anatomy). Later the findings of right-sided CDH were illustrated in detail by Jan van Rymsdyk[10]. In 1761 Giovanni Battista Morgagni described different localizations of CDH and presented an older patient with a ventral defect – that later was referred to as Morgagni's hernia. As Raffensperger[11] points out, Vincenz Alexander Bochdalek described the pleuroperitoneal canal and recognized the increased incidence of left-sided defects in 1848. In his opinion, "practical surgery" was the only way to cure. The dorso-lateral diaphragmatic defect is nowadays referred to as Bochdalek's hernia.

In 1847 (published 1853) Henry Bowditch presented the first case-series of 68 patients with diaphragmatic hernia (26 congenital cases) and described clinical criteria for diagnosis. He defined three categories of CDH: "1st. Those who die at birth or immediately afterward. 2d. Those who live for a few months, or years, in a state of more or less constant ill health. 3d. Those who arrive at the adult age, and are able to perform many of the duties of life, even those, at times involving the hardest kind of labor"[12].

In 1868 Dr. Thomas Balfour described several associated congenital malformations that had been observed with congenital diaphragmatic hernia in fetuses and neonates (e.g. spina bifida, omphalocele, harelib, undescended testis, limb malformations, anencephalus) and mentioned thoracic asymmetry as one sign in older children. He also further classified congenital diaphragmatic hernias into: "1st, Those cases in which the viscera have not passed through the diaphragm, but have simply pushed that muscle with the peritoneum and pleura before them into the thorax, thus causing a hernial protrusion. 2d, Those in which the passage through the diaphragm has been effected by an abnormal opening caused by a deficiency of muscular structure. 3d, Those in which a *normal* opening has been enlarged as to allow the transmission through it of the abdominal viscera. 4th, Those cases in which the hernial protrusion has been accomplished by a separation of the muscular fibres. 5th, Those where the viscera pass into the thorax through those portions of the diaphragm where there is *naturally* an absence, or, at least, great paucity, of muscular fibres.' He also differentiated between patients with and without a hernial sac and noted, that most patients do not have a hernial sac"[13].

Irish[14] also refers to the history of surgical repair: The first suggestion for reduction of the intestines from the thoracic cavity via a laparotomy was made by René Théophile Hyacinthe Laënnec (1781-1826) and again proposed by Bowditch and Bochdalek.

[10] Cullis and Davis (2018)
[11] Raffensperger (2018)
[12] Irish et al. (1996)
[13] Balfour (1869)
[14] Irish et al. (1996)

The first attempt of surgical repair via laparotomy was made by Naumann in 1888 in a 19-year-old patient with incarcerated intestines, but the patient died due to septicaemia. One year later Joseph O'Dwyer operated on a 3 ½ year old child, that died a few hours after surgery. He postulated that death was due to an increased intraabdominal pressure. In 1905 L. Heidenhain reported on a successful CDH-repair in a 9-year-old child via median laparotomy, that was performed in 1902.

In his book on the technique of urgent operations published in 1904, Hans Strehl also differentiates between acquired and congenital diaphragmatic hernia. He emphasizes that symptoms of congenital diaphragmatic hernia in adulthood are mostly related to intestinal obstruction without evident cause. He emphasizes the importance of early laparotomy and meticulous investigation of the diaphragm. If a diaphragmatic defect can be identified, he recommends to rather close the diaphragmatic defect via a thoracotomy after partial resection of the ninth rip. He also describes that there is usually no hernial sac. Resection should be performed in gangraeneous intestine, because he considers the "anus praeter naturalis pleuralis" as a bad solution. A drain should be put only, if the content of the pleural cavity or the condition of the prolapsed viscera necessitate it[15].

Among 378 cases of diaphragmatic hernia collected from literature and personal experience C.A. Hedblom published 44 patients with CDH in 1925, and observed that 75% of untreated neonates died within the first month of life. He therefore concluded, that early surgery would be beneficial regarding survival. In 1929 R.B. Bettman and J.H. Hess reported on a successful operation in a 3 ½ months old child with incarcerated CDH via thoracotomy and median laparotomy. The defect was closed after fracture of the ribs to reduce defect size. At the same time H.M. Greenwald and M. Steiner described survival in five of eleven operated patients. In 1940 William E. Ladd and Robert E. Gross reported, that nine out of sixteen children survived (56%), in whom diaphragmatic reconstruction was performed. They concluded, that early surgery would be beneficial due to less distended intestine and therefore easier reduction into the abdominal cavity. The first successful neonatal repair of CDH below 24 hours of age was achieved in 1946 also by Robert E. Gross. He suggested a transabdominal surgical approach for neonates and also advised delayed closure of the rectus fascia, if having difficulty to close the abdominal cavity after diaphragmatic reconstruction.

The paradigm of emergency surgery was shifted to delayed surgery, after E.T. Boles had shown in 1971, that mortality in neonates could be lowered from 76% to 28% after preoperative stabilization with intratracheal intubation, ventilation, insertion of a nasogastric tube, intravenous fluid management via a central venous line and warming of the children[16].

[15] Lejars and Strehl (1904)
[16] Boles et al. (1971)

Better understanding of pathophysiology has changed the opinion about congenital diaphragmatic hernia: it “is more a physiologic than a surgical disease”[17]. Since then, therapeutic advances in prenatal and neonatal care have led to an increased survival rate especially in high-volume centres[18] and publications today are rather focussing on long-term-morbidity and follow-up of these children[19] – to enhance outcome by optimized therapeutic strategies.

Minimally-invasive techniques were first applied for correction of congenital diaphragmatic hernia in 1995: thoracoscopy in an adolescent by Silen[20] and laparoscopy in an infant by van der Zee and Bax[21]. The first successful thoracoscopic repair in a neonate was reported by Liem in 2003[22].

In 1995 the CDH-Study Group was founded in the U.S. to collect multicentre data of CDH-neonates until discharge from their first hospital stay into a registry. In 2008 The CDH-EURO-Consortium was founded by high-volume-centres in Europe to develop standardized postnatal treatment guidelines[23] and conduct studies to better understand this rare disease and improve outcome[24].

[17] Muratore and Wilson (2000)
[18] Frenckner et al. (1997); Skari et al. (2004); Grushka et al. (2009)
[19] Hollinger et al. (2017); IJsselstijn et al. (2017); Morini et al. (2017); IJsselstijn et al. (2018)
[20] Silen et al. (1995)
[21] van der Zee and Bax (1995)
[22] Liem (2003)
[23] Reiss et al. (2010); Snoek et al. (2016b)
[24] Deprest et al. (2005); van den Hout et al. (2011)

1.3 Embryology

The diaphragm develops between the fourth and 12th week of gestation. The transverse septum grows from ventral to dorsal and separates the pleurocardial from the peritoneal cavity. The pleuroperitoneal canal is closed in the 8th week by fusion of the transverse septum with the esophageal mesentery[25]. The pleuroperitoneal folds consist of membranous pleura and peritoneum, while migration of muscle cells occurs later[26]. Left-sided and dorsal defects are more common, because of the growth-direction of the transverse septum. If the pleuroperitoneal canal persists, a Bochdalek hernia results (90%). Anterior defects are much rarer: Morgagni-hernia on the right side and Larrey-hernia on the left side[27].

If migration of myogenous cells is reduced or absent, the pleuroperitoneal membrane persists and results in a hernial sac covering the prolapsing abdominal viscera. Muscle hypoplasia results in eventration of the diaphragm[28].

Abnormal lung development can be explained by the dual-hit hypothesis: Genetic and epigenetic disturbances during embryonic development and environmental factors lead to a ‚first hit' during organogenesis: both lungs show abnormal development and the diaphragm does not develop properly.

The ‚second hit' only affects the ipsilateral lung and can be explained by disturbed fetal breathing efforts: the larger the diaphragmatic defect, the earlier in pregnancy abdominal viscera herniate into the thoracic cavity, cause compression of the ipsilateral lung and thus compromise fetal breathing efforts[29].

In most congenital anomalies structural changes exist in one system that also cause further anomalies in other systems. The structural defect of the diaphragm and heart is part of a genetic syndrome and influences pulmonary development and function[30].

Most diaphragmatic hernias develop sporadically (70%). In about 20% the influence of toxins (thalidomid or nitrofen) and a vitamin-A-deficiency are discussed[31]. In 10% an underlying syndrome can be diagnosed (e.g. trisomy 18 or 21, Turner-syndrome, Wiedemann-Beckwith-syndrome, VACTERL-association, Pallister-Kilian-syndrome, Denys-Drash-syndrome, Fryns-syndrome, Marfan-syndrome, Simpson-Golabi-Behmel-syndrome, Cornelia-(Brachmann)-de-Lange-syndrome, Wolf-Hirschhorn-syndrome)[32].

[25] Keijzer and Puri (2010); Merrell and Kardon (2013); Kardon et al. (2017)
[26] Babiuk et al. (2003); Merrell and Kardon (2013); Kardon et al. (2017)
[27] Kays (2006); Deprest et al. (2005); Kardon et al. (2017); Rottier and Tibboel (2005); Dahlheim et al. (2003)
[28] Waag et al. (2008); Kardon et al. (2017)
[29] Kardon et al. (2017); Jesudason et al. (2000); Keijzer et al. (2000)
[30] Abman et al. (2015)
[31] González-Reyes et al. (2005); Chandrasekharan et al. (2017)
[32] Graham and Devine (2005); Kardon et al. (2017)

1.4 Pathophysiology

During early organogenesis a reduced division of bronchi and rarefication of pulmonary vasculature in both – the ipsi- and contralateral lung can be observed. Histologically a hypertrophy of smooth muscle cells and consecutive hyperplasia of the media also in peripheral arterioles is detected[33]. All of these changes can also be observed in the contralateral lung but in a less severe manifestation (double-hit hypothesis)[34]. Vascular remodelling with hyperplasia of the media contributes to the irreversible cause of pulmonary hypertension[35]. Additionally, a change in vasoreactivity is a reversible cause: this can be due to an imbalance of autonomous innervation with increased sympathetic tone[36] or a reduced endothelium-derived relaxation of pulmonary arteries[37]. Also, an imbalance of vasoconstricting and vasodilating mediators has been described[38]. Neonates with small diaphragmatic defects or with a hernial sac only rarely suffer from severe pulmonary hypertension with optimal postnatal treatment.

Severe pulmonary hypertension results in hypertrophy of the right ventricle and reduced left ventricular output due to persistent fetal circulation with right-left-shunting via the persisting PDA and foramen ovale. Left ventricular failure results in an elevation of left atrial pressure and pulmonary venous stasis, which aggravates pulmonary hypertension[39]. Decreased left-ventricular cardiac output is strongly associated with the need for ECMO-therapy and has been shown to be a better predictor than severity of pulmonary hypertension and right-ventricular dysfunction[40]. Nitric oxide (NO) and prostaglandines cause dilatation of the pulmonary vessels, which reduces right-ventricular afterload and enhances circulatory flow[41]. Postnatally a refractory pulmonary hypertension may develop due to a combination of the above mentioned pathomechanisms and an extracorporeal membrane oxygenation (ECMO-) therapy may be necessary to overcome the reversible causes of pulmonary hypertension. Mortality and need for ECMO-therapy can be predicted within 12 hours after birth by postnatal parameters using the Neonatal Acute Physiology-II-score (SNAP-II-score) in neonates with a gestational age of at least 34 weeks: According to mean blood pressure, body temperature, the ratio of pO_2:FiO_2, lowest serum pH, presence of multiple seizures and urine output a score is calculated from a minimum of 0 points to a maximum of 115. The worst values of these parameters lead to the highest score[42].

[33] Kitagawa et al. (1971); Shehata et al. (1999); Lakshminrusimha (2012)
[34] Merrell and Kardon (2013); Kardon et al. (2017)
[35] Montalva et al. (2019)
[36] Lath et al. (2012)
[37] Schmidt et al. (2013)
[38] Lath et al. (2012); Shinkai et al. (2005)
[39] Siebert et al. (1984); Byrne et al. (2015); Patel and Kipfmueller (2017)
[40] Gaffar et al. (2019)
[41] Inamura et al. (2005); Kinsella et al. (2005); Lawrence et al. (2019)
[42] Snoek et al. (2016a)

1.5 Prenatal diagnosis

CDH as well as further associated anomalies, that have an impact on survival and prognosis, can be detected on prenatal ultrasound[43]. The antenatal detection-rate of CDH in ultrasonography is about 80%[44], because differentiation of lung and liver can be challenging due to a similar echogenicity especially in right-sided CDH[45]. This may be easier on antenatal MRI[46].

Different prognostic factors were identified for both investigative procedures: In ultrasonography the lung-to-head-ratio (LHR) was established. The longest axis of the contralateral lung is multiplied by the longest diameter perpendicular to it and this is divided by the head circumference[47]. The smaller the ratio the less likely is survival and the more likely are long-term sequelae[48]. Therefore, patients with a LHR below 1.4 should be transferred in utero to a tertiary centre for optimized postnatal care[49]. But the measurements have a relatively high inter- and intra-observer-variability and values change with gestational age, because normal lung size increases more than head circumference during gestation[50]. Therefore the ‚observed-to-expected lung-to-head-ratio' (o/e LHR) was developed, which gives the percentage of LHR of the affected fetus in relation to the median expected LHR of a healthy fetus of the same gestational age[51].. These values have been shown to change little with ongoing pregnancy and therefore have a good prognostic value in regards to survival and chronic lung disease[52].

On antenatal MRI-scans the fetal lung volume can also be determined and the observed-to expected fetal lung volume (o/e FLV) can be calculated. Comparative studies for normal fetal lung volume at certain gestational ages have been performed and different formulas to calculate the o/e FLV have been published[53]. Recent studies have shown a significant correlation of o/e LHR and o/e FLV around 32 WOG in left-sided CDH but only a weak correlation in right-sided CDH[54].

[43] Wessel et al. (2015)
[44] Losty (2014)
[45] Burgos et al. (2018)
[46] Kilian et al. (2006); Marlow and Thomas (2013)
[47] Metkus et al. (1996)
[48] Graham and Devine (2005); Hedrick et al. (2004); Reiss et al. (2010); Snoek et al. (2016b); Snoek et al. (2017)
[49] Waag et al. (2008)
[50] Peralta et al. (2006); Peralta et al. (2005); Jani et al. (2006)
[51] Jani et al. (2007a); Ba'ath et al. (2007)
[52] Jani et al. (2007b); Snoek et al. (2017)
[53] Büsing et al. (2008); Mayer et al. (2011)
[54] Kastenholz et al. (2016)

O/e FLV on antenatal MRI has also been shown to be a significant prognostic marker in l-CDH regarding survival, need for postnatal ECMO-therapy, development of chronic lung disease (CLD)[55] and necessity for diaphragmatic patch implantation[56]; see table 1.
In left-sided CDH herniation of the left liver-lobe ('liver-up') also is a significant prognostic marker for survival, need for postnatal ECMO-therapy and chronic lung disease[57].

Table 1: observed-to-expected fetal lung volume on antenatal MRI is a prognostic marker regarding survival, need for postnatal ECMO-therapy, development of CLD[58] and necessity for diaphragmatic patch implantation[59]

parameter	number of patients	o/e FLV on MRI (%)	p-value
survival	218	32.01 ± 12.45	<0.0001
no survival	52	21.24 ± 9.18	
ECMO-therapy	102	23.87 ± 8.79	<0.0001
no ECMO-therapy	168	33.62 ± 13.17	
CLD	127	26.30 ± 9.04	<0.0001
no CLD	100	38.78 ± 12.92	
patch	190	27.7 ± 10.2	<0.001
no patch	57	40.8 ± 13.8	

There are limitations to sonographic investigation in cases of maternal obesity and in suboptimal intrauterine fetal position, but ultrasonography has a broader availability than MRI and is therefore a valuable primary diagnostic tool. The o/e FLV on antenatal MRI and the o/e LHR on antenatal ultrasound show a significant association[60]. Nevertheless, MRI-investigation seems to be more accurate in predicting survival as well in right- as in left-sided CDH, shows a higher detection-rate of intrathoracic liver-herniation and the o/e FLV is a better independent predictor of postnatal survival[61].

[55] Kastenholz et al. (2016)
[56] Hagelstein et al. (2015)
[57] Walleyo et al. (2013); Schaible et al. (2012); Debus et al. (2013); Weis et al. (2018)
[58] Kastenholz et al. (2016)
[59] Hagelstein et al. (2015)
[60] Victoria et al. (2012)
[61] Marlow and Thomas (2013); Jani et al. (2009)

In a comparative study of 85 fetuses with isolated l-CDH an intrathoracic liver-herniation and the o/e FLV on MRI were significant antenatal indicators for survival after birth in multivariate analysis, while o/e LHR was not[62]. MRI-determined parameters showed the best combination of sensitivity and specificity and therefore seem to offer a better predictive value[63].
Antenatal risk-stratification shall guide perinatal management (e.g. fetoscopic tracheal occlusion (FETO) therapy), place of delivery (e.g. ECMO-centre) and mode of delivery to enhance survival and reduce the risk of long-term-morbidity[64].

1.6 Intrauterine therapy

High-risk patients are neonates with antenatal diagnosis on ultrasonography before 25 WOG, ‚liver-up' in left-sided CDH, low o/e LHR on ultrasound or low o/e FLV on MRI, hypoplastic left ventricle, low birth weight and fetal hydrops. In selected cases of severe and moderate left-sided CDH a temporary fetoscopic tracheal occlusion was performed in the multi-centre randomized-controlled TOTAL-trial (Tracheal Occlusion To Accelerate Lung growth)[65]. Previous studies have shown an improved survival rate in fetuses with an LHR <1.0 and bad prognosis after the trachea of the fetus had been temporarily blocked with a fetoscopically inserted balloon[66]. There is an increased risk of preterm labour and preterm delivery[67]. In patients with moderate CDH there was no apparent benefit regarding survival or the need for oxygen at six months of age but in patients with severe CDH there was a significant better outcome[68].

1.7 Clinical symptoms

Symptoms after birth depend on the size of the diaphragmatic defect, associated lung hypoplasia and severity of pulmonary hypertension. Only 5% of children will become symptomatic later in life or the diagnosis is made incidentally e.g. on a chest X-ray to rule out pneumonia. These children usually only have a small diaphragmatic defect and abdominal viscera may as well herniate postnatal due to an increased intraabdominal pressure (e.g. coughing, crying, fall). Therefore, these patients do not suffer from relevant lung hypoplasia.
The majority of patients with CDH will become symptomatic directly after birth or within infancy. Primary symptoms in neonates are tachypnea/dyspnea, cyanosis due to right-left-shunting via

[62] Victoria et al. (2012)
[63] Bebbington et al. (2014)
[64] Frenckner et al. (2007); Reiss et al. (2010); Snoek et al. (2016b)
[65] Deprest et al. (2009); Deprest et al. (2014); Basurto et al. (2019)
[66] Harrison et al. (2003); Deprest et al. (2004); Deprest et al. (2005); Kohl et al. (2006)
[67] Jani et al. (2009)
[68] Deprest et al. (2021a); Deprest et al. (2021b)

PDA and PFO, collapsed abdomen, intrathoracic peristaltic sounds on the ipsilateral side, absent or diminished breath sounds on the ipsilateral side, mediastinal shift with auscultation of heart sounds on the contralateral side and pre- and postductal difference of oxygen saturation. If mask ventilation is applied in neonates with unknown CDH and respiratory distress, symptoms will aggravate due to intrathoracic intestinal distension and worsening of lung compression and mediastinal shift[69]. Sometimes patients are relatively asymptomatic in the first few hours while breathing spontaneously and then develop respiratory distress syndrome. This stable phase is called ‚honeymoon'. Then oxygenation deteriorates due to aggravation of pulmonary hypertension[70]. Patients with a decompensated respiratory situation or suprasystemic pulmonary hypertension consequently develop cyanosis.

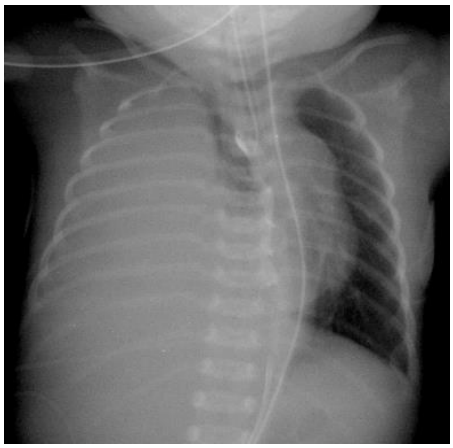
Secondary symptoms in infancy are tachypnea and dyspnea during physical efforts (e.g. drinking with interruptions, nasal flaring, chest wall retractions), chronic or recurrent abdominal pain as signs of intermittent incarceration, constipation, gastro-esophageal reflux, ipsilateral peristaltic sounds on auscultation, mediastinal shift to the contralateral side and absent or diminished breath sounds on the ipsilateral side.

1.8 Postnatal diagnostics

If CDH is suspected from the symptoms on clinical investigation, the diagnosis can be confirmed by a plane chest X-ray. This will show insufflated bowel loops in left-sided CDH and more often opacity in right-sided CDH. If a nasogastric tube was placed, an intrathoracic herniation of the stomach may also become evident. The ipsilateral lung is small and may only be seen in the thoracic apex. Additionally, a mediastinal shift to the contralateral side can be identified[71] (figure 1). Vertebral anomalies may also be detected incidentally.
In delayed and atypic presentation of CDH a contrast-study of the intestinum can be helpful.

To detect associated anomalies also a cardiac, renal and cerebral ultrasound should be performed. Especially malformations of the limbs, facial dysmorphisms, spina bifida, imperforate anus or genital malformations may also become evident on clinical investigation. In cases with multiple congenital anomalies genetic testing is advisory to rule out fatal syndromes (e.g. trisomy 13 or 18).

[69] Waag et al. (2008)
[70] Chandrasekharan et al. (2017)
[71] Waag et al. (2008)


1.1


1.2

Figure 1: plane chest X-ray of neonates: 1.1 right-sided CDH: opacity of right hemithorax, mediastinal shift to the left; 1.2 left-sided CDH: insufflated bowel-loops in left hemithorax, stomach-up (nasogastric tube), mediastinal shift to the right

1.9 Postnatal neonatal therapy

According to the CDH-EURO-Consortium consensus[72] and its update[73] a standardized treatment algorithm exists for postnatal neonatal therapy:

1.9.1 Mode of delivery

In patients with an estimated good prognosis (LHR >1.8) a vaginal delivery can be awaited. In more severely affected neonates (LHR<1.5) a Caesarean section should be performed to avoid prolonged stress and aggravation of pulmonary hypertension during birth[74]. Delivery should not be planned preterm but term because of better survival-rates[75].

1.9.2 Intubation and Ventilation

The neonate should be primarily intubated to reduce respiratory distress and consequently insufflation of the gastrointestinal tract. Mask ventilation has to be avoided, because insufflation of the gastrointestinal tract aggravates mediastinal shift and compression not only of the ipsi- but also of the contralateral lung – thus aggravating ventilatory problems and also pulmonary hypertension. Ventilation should be performed as ‚gentle ventilation' with a maximum peak inspiratory pressure (PIP) below 28 cmH_2O to reduce barotrauma to the lungs. An elevated level of carbon dioxide is tolerated in the first hours (‚permissive hypercapnia'), because it was shown to improve survival[76].

[72] Reiss et al. (2010)
[73] Snoek et al. (2016b)
[74] Reiss et al. (2010); Frenckner et al. (2007)
[75] Burgos et al. (2017a)
[76] Boloker et al. (2002); Baquero et al. (2006); Greenspan and Shaffer (2006); Migliazza et al. (2007); Guidry et al. (2012)

High frequency oscillation ventilation was shown not to be superior to conventional ventilation regarding survival and incidence of bronchopulmonary dysplasia (BPD) in CDH-neonates within the VICI-trial. Regarding ventilation time and need for extracorporeal membrane oxygenation (ECMO), conventional ventilation even seemed more favourable[77].

1.9.3 Administration of surfactant

There is no evidence for an advantage of administration of surfactant in neonates with congenital diaphragmatic hernia[78]. Prophylactic administration was even associated with a higher mortality in preterm patients[79]. Neonates with CDH and substitution of surfactant were observed to have a higher rate of ECMO-therapy, a higher incidence of chronic lung disease (CLD) and a higher mortality[80].

1.9.4 Medical treatment of pulmonary hypertension

Inhaled NO (iNO) should be started with 20 ppm (parts per million), if the difference between pre- and postductal O_2-saturation exceeds 10% to reduce pulmonary hypertension and right-left-shunting by vasodilatation of the pulmonary arteries. Also, prostaglandine E1 and prostacyclin reduce pulmonary hypertension by relaxation of the smooth muscle cells in pulmonary arteries and thus vasodilatation[81]. They may be added to iNO-therapy, if iNO by itself does not reduce pulmonary hypertension sufficiently[82]. Sildenafil (Viagra®) is usually given for treatment of chronic pulmonary hypertension[83]. There will be a prospective trial conducted by the CDH-EURO-Consortium to investigate the effects of inhaled NO compared to intravenous Sildenafil as primary treatment of pulmonary hypertension in CDH-neonates (CoDiNOS-trial).

1.9.5 Medical treatment

Furthermore, an adequate fluid-management to maintain sufficient diuresis (>1ml/kg/hour) has to be established. Inotropic or vasopressor support has to be considered in persisting hypotension – the advantage of suprarenin is its increase of systemic arterial resistance without increasing pulmonary vascular resistance. Additionally, analgosedation with fentanyl and midazolam reduces oxygen consumption and is therefore recommended[84]. The administration of muscle relaxants is being discussed controversial[85].

[77] van den Hout et al. (2011)
[78] Zimmermann et al. (2005)
[79] van Meurs (2004); Lally et al. (2004)
[80] Reiss et al. (2010)
[81] Chandrasekharan et al. (2017); Lawrence et al. (2019)
[82] Ehlen and Wiebe (2003); Luca et al. (2006)
[83] Lakshminrusimha et al. (2016)
[84] Carbajal et al. (2007); Durrmeyer et al. (2013)
[85] Reiss et al. (2010)

1.9.6 ECMO-therapy

In extracorporeal membrane oxygenation (ECMO) blood is drawn from the newborn via the cannulated right jugular vein, oxygenated in an extracorporeal circuit, warmed and re-infused into the patient. Thus, ventilation parameters can be reduced to avoid barotrauma of the lungs and the reversible factors of pulmonary hypertension may be overcome (chapter 1.4: Pathophysiology). Treatment criteria have been defined in the CDH-EURO-Consortium consensus[86]: ECMO-therapy should be initiated, if a preductal O_2-saturation >85% and a postductal saturation of >70% cannot be maintained, CO_2 rises besides optimized ventilation or the ventilatory settings exceed a PIP of 28 cmH_2O or a mean airway pressure (MAP) of 17 cmH_2O. Also, circulatory reasons such as metabolic acidosis with inadequate oxygen-exchange (lactate >5mmol/l; pH<7.2) or persistent hypotension despite adequate volume substitution and administration of vasoactive medication can necessitate ECMO-therapy.

Its use is discussed controversially in literature and there have been no trials so far to prove its efficacy. Nevertheless, centres offering ECMO-therapy noticed an increased survival-rate but these results may also be biased by the fact, that these centres have a higher expertise due to a higher number of patients treated per year[87]. Contraindications to commence ECMO-therapy are severe lung hypoplasia (PaO_2 <40 mmHg, $PaCO_2$ >100 mmHg), low birth weight (<1800 g) due to small vessels and inability to establish an adequate flow on ECMO and prematurity due to an increased risk of haemorrhage with necessary anticoagulation.

ECMO-therapy can be conducted as veno-venous or veno-arterial ECMO. In veno-venous ECMO a double-lumen cannula is inserted into the right jugular vein, while in veno-arterial ECMO the right jugular vein and common carotid artery are cannulated. Veno-arterial ECMO seems to be more favourable in CDH-neonates, because it also reduces cardiac workload, which is especially important in patients with a hypoplastic left ventricle. After decrease of pulmonary hypertension, recruitment of the lungs and possible reduction of ECMO-runs to 20% of cardiac output ECMO-therapy can be terminated after an idling phase.

[86] Reiss et al. (2010); Snoek et al. (2016b)
[87] Reiss et al. (2010); Davis et al. (2012); Yoder et al. (2012); Zalla et al. (2015); Kays (2017); Grover et al. (2018)

1.10 Surgical therapy

1.10.1 Reconstruction of the diaphragm

Nowadays, surgery is performed as delayed surgery after sufficient stabilization of the neonate[88]. Nevertheless, it has been shown by the CDH study group that „timing of repair in low-risk infants does not seem to influence mortality“ [89]. Different approaches are possible: access can be obtained via abdomen or thorax and open or minimally invasive techniques are available. In large diaphragmatic defects reconstruction of the diaphragm may only be achieved by implantation of prosthetic patches[90] or muscle flaps[91], while in smaller defects a primary repair either by open[92] or minimally invasive surgery (MIS)[93] can be accomplished. A subcostal incision is preferred for laparotomy by most surgeons and it has been reported that a primary repair is possible in 60-70% of cases[94]. If a diaphragmatic substitute is necessary, different shapes and materials have been used for patch implantation (absorbable and non-absorbable)[95]. In the future implantable diaphragms may even be constructed by tissue-engineering[96]. A more detailed description of the different techniques to achieve reconstruction of the diaphragm in our cohort is given in chapter 2.1 and the different approaches are discussed in chapter 4.5 and 4.6.

1.10.2 Reconstruction of the abdominal wall

Especially in large diaphragmatic defects the abdominal cavity is hypoplastic, because most abdominal organs herniated into the thoracic cavity, and neonates present with a collapsed abdomen. This has to be taken into account during surgery and closure of the abdomen: in some cases implantation of an abdominal wall patch may be necessary to prevent abdominal compartment syndrome and compromise of intestinal and renal perfusion[97]. Also, a staged repair with secondary closure of the abdomen has been proposed in large diaphragmatic hernia[98].

[88] Reiss et al. (2010); Snoek et al. (2016b)
[89] Harting and Lally (2007)
[90] Saxena (2018)
[91] Brant-Zawadzki et al. (2007)
[92] Spitz and Coran (2006)
[93] Gomes Ferreira et al. (2009)
[94] Losty (2014)
[95] Harting and Lally (2007)
[96] Urita et al. (2008); Fauza (2014); Gubareva et al. (2016); Zhang et al. (2018); Trevisan et al. (2019)
[97] Maxwell et al. (2013); Barroso and Correia-Pinto (2018)
[98] Laje et al. (2016)

1.11 Mortality and Morbidity

1.11.1 Mortality

Initially, the correction of CDH was thought to necessitate an immediate operation after birth to reposition the abdominal viscera and reduce compression of the lungs. In neonates mortality was as high as 76%[99]. The introduction of ECMO therapy seemed to improve survival[100]. Changing the paradigm of surgery for CDH from an emergency intervention to delayed surgery after stabilization of the neonate led to increased survival rates[101]. Milestones were rising experience in neonatal intensive care and the introduction of ‚gentle ventilation', permissive hypercapnia, inhaled NO, ECMO therapy and medical treatment of pulmonary hypertension[102]. Still varying survival rates are reported by different centres[103], but in general better results are reached in high-volume centres[104]. Survival correlates with associated anomalies[105] and defect size[106], consecutive lung-hypoplasia[107], pulmonary hypertension[108] and position of liver[109] and stomach[110] in left-sided CDH.

1.11.2 Surgical complications

Children who survive to delayed surgical reconstruction of the diaphragmatic defect may encounter different postoperative complications. In case of sudden deterioration postoperatively a *pneumothorax* has to be excluded or – if confirmed – drained by a thoracic tube[111]. An irrelevant *pleural effusion* usually develops after reconstruction of the diaphragm with absorption of the intraoperatively trapped air and prolonged expansion of the hypoplastic lung[112]. If lymphatic vessels or the thoracic duct were injured during surgery, a *chylothorax* develops. The incidence has been reported to be as high as 28%[113]. There is a multimodal therapeutical approach: pleural drain and substitution of volume, FFP and proteins, while waiting for spontaneous resolution. In severe cases a reduction of intestinal fat absorption by a special diet and the administration of somatostatine may be necessary. In massive loss of

[99] Boles et al. (1971)
[100] Weber et al. (1998)
[101] Boles et al. (1971); West et al. (1992)
[102] Boloker et al. (2002)
[103] Snoek et al. (2018)
[104] Grushka et al. (2009); Davis et al. (2012); Hayakawa et al. (2013); Chandrasekharan et al. (2017)
[105] Menon et al. (2013)
[106] Lally et al. (2013)
[107] Neff et al. (2007)
[108] Dillon et al. (2004); Wynn et al. (2013)
[109] Mullassery et al. (2010)
[110] Cordier et al. (2015)
[111] Waag et al. (2008)
[112] Barroso and Correia-Pinto (2018)
[113] Kavvadia et al. (1998); Dahlheim et al. (2003); Loff et al. (2005); Levy et al. (2013)

chyle, a capillary leak syndrome and ultimately death may result. In some patients a congenital chylothorax exists already at the time of surgery and its aetiology is not well understood.
In large defects crura and diaphragm are hypoplastic and *gastroesophageal reflux* may result also due to gastrointestinal dsymotility[114]. In our cohort the incidence was reduced after implantation of a cone-shaped patch and no further benefit of primary prophylactic fundopexy could be noted[115]. In cases of severe GER a jejunal feeding tube and secondary hiatoplasty and fundoplication have to be considered, its incidence being reported to be as high as 60%[116].
Early recurrence within the first hospital-stay has been reported from the CDH registry in 2.7% in open surgery and 7.9% in MIS[117]. A higher early recurrence rate after MIS was confirmed by Putnam in 2017[118].

1.11.3 Long-term morbidity

Long-term morbidity is influenced by genetic changes, that can be detected in 30-40% of patients[119]. *Lung hypoplasia* persists life-long[120]. Children who underwent ECMO therapy show an impaired lung function testing at the age of 6 years, especially concerning forced expiratory flow at one second (FEV1)[121]. Also, obstructive and restrictive ventilation disorders can be detected[122]. Due to ventilation induced barotrauma of the lungs, up to 41% of patients suffer from *bronchopulmonary dysplasia* (BPD) with persistent O_2-dependency[123]. Meanwhile the nomenclature has changed and prolonged oxygen-dependency longer than 28 days is now referred to as *chronic lung disease* (CLD)[124].

It could be shown that patients with initial intrathoracic liver-position in left-sided CDH and necessity for patch repair of the diaphragmatic defect have a worse pulmonary outcome[125] and that exercise capacity deteriorates reaching puberty independent of neonatal ECMO therapy[126].

[114] Tovar (2012)
[115] Maier et al. (2011)
[116] Bagolan and Morini (2007)
[117] Tsao et al. (2011)
[118] Putnam et al. (2017)
[119] Moss et al. (2001); Cortes et al. (2005); Chen et al. (2007); Veenma et al. (2012); Wynn et al. (2013)
[120] Muratore et al. (2001); Ameis et al. (2017)
[121] Dahlheim et al. (2003)
[122] Stefanutti et al. (2004); Trachsel et al. (2005)
[123] Greenough and Khetriwal (2005); Greenspan and Shaffer (2006); Muratore et al. (2001); van den Hout et al. (2010)
[124] Snoek et al. (2017)
[125] Tan et al. (2019); Wigen et al. (2019)
[126] Toussaint-Duyster et al. (2019)

Pulmonary hypertension may persist and long-term therapy with sildenafil, diuretics and/or oxygen may be necessary[127]. *Pulmonary infections* can aggravate pulmonary hypertension and should therefore be avoided. Passive immunization is available to prevent severe bronchiolitis due to RSV-infection.

Due to lung hypoplasia respiratory effort and thus caloric requirements are increased especially in the first two years of life. Children might therefore *fail to thrive*, especially more severely affected patients after ECMO therapy and patients, who suffer from oral aversion due to GER or after long treatment on the intensive care unit[128].

Furthermore, gastrointestinal problems such as *GER*[129] and *motility disorders* due to adhesions are common complications[130]. Symptomatic reflux is treated with antireflux medication and in more severe cases with hiatoplasty and fundoplication. The incidence of GER has been reported to be significantly higher in patients, who underwent patch repair of the diaphragmatic defect[131]. In general, the incidence of GER is probably underestimated[132]. *Gastrointestinal dysmotility* can also be associated with sedation, relaxation, detoxification after long-term-sedation and septicaemia and therefore time to full enteral feeds may be prolonged.

With growth a recurrent diaphragmatic defect may develop as *late recurrence* that requires secondary surgery – because it always bears the risk of intestinal incarceration, bowel gangrene and lethal septicaemia, if not diagnosed and treated appropriately. Due to its slow development symptoms may be variable and unspecific. Therefore, a structured follow-up-program until adolescence with regular radiological imaging has been established at our hospital for all CDH-patients to reliably detect recurrence.

Lung hypoplasia can cause *funnel chest* due to increased respiratory effort in the beginning. In more relevant lung hypoplasia funnel chest may persist and *thoracic asymmetry* and *scoliosis* may develop. Orthopaedic sequelae also seem to be correlated to CDH-severity[133].

[127] Abman et al. (2015); Gien and Kinsella (2016)
[128] Dahlheim et al. (2003); Peetsold et al. (2009); [128] Tan et al. (2019)
[129] Tan et al. (2019)
[130] Yokota et al. (2014); Janssen et al. (2017); Barroso and Correia-Pinto (2018)
[131] Valfrè et al. (2011)
[132] Peetsold et al. (2010); Morandi et al. (2016); Zanini et al. (2017)
[133] Antiel et al. (2016); Takayasu et al. (2016); IJsselstijn et al. (2018)

Neurodevelopmental retardation has also been reported[134] and could be correlated to severity of CDH[135]. Deficits of motor function and speech have been observed especially after a long ventilation time[136]. ECMO therapy and the necessity for diaphragmatic reconstruction with a patch have been identified as risk factors[137].

With increased survival and significant long-term morbidities very recent studies also focus on *quality of life* in CDH-survivors. In a matched-control-study from Australia total difficulties score was significantly higher and objective quality of life significantly lower in CDH-patients born 1993 to 2008[138]. On the other hand, reassuring quality of life scores were reported by 46 parents of CDH-patients born 2007 to 2014 and no difference could be detected concerning type of diaphragmatic repair, side of CDH, ECMO therapy or recurrence. But there seemed to be a correlation between older age and worse school function[139]. Another study also did not find a significant difference between CDH-patients and healthy children. But they identified a significantly lower health related quality of life score to be correlated to an increased family impact score and the need for special education[140].

[134] Tan et al. (2019)
[135] Danzer et al. (2010); Danzer and Hedrick (2011); Danzer et al. (2013a); Danzer et al. (2013b); Antiel et al. (2017); Grover et al. (2018)
[136] Snoek et al. (2017)
[137] Danzer et al. (2010); Danzer et al. (2013b)
[138] Tan et al. (2019)
[139] Morsberger et al. (2019)
[140] Fritz et al. (2019)

1.12 Aim of the study

Surgical repair of congenital diaphragmatic hernia (CDH) in the neonatal period is up to now an intervention with a high rate of complications. Improvement of pre-, peri- and postnatal care have enhanced survival rates and thus long-term morbidity gains more and more importance. Surviving children may be affected by oxygen dependency due to lung hypoplasia and persistent pulmonary hypertension, recurrent pulmonary infections, feeding and various gastro-intestinal problems, failure to thrive, orthopaedic or neurological side effects and a therefore reduced quality of life. Among intestinal obstruction caused by adhesions, recurrence is the most severe surgical complication.

Different surgical techniques have been described in literature to achieve closure of the diaphragmatic defect. In patients with smaller defects and a broad muscular rim primary closure is possible. In patients with large defects either a muscular flap or synthetic patches are required as a diaphragmatic substitute. Different absorbable and non-absorbable materials have been introduced and different suture techniques or shapes of these patches have been described[141].

In all techniques, recurrence after surgical repair of CDH is a common complication in survivors in the long-term. Due to their slow development diaphragmatic complications may as well be asymptomatic in most patients. Intermittent upper abdominal pain or vomiting, gastroesophageal reflux (GER), a change in eating habits and stooling frequency may be other hints - but these symptoms are mild and unspecific and often only reported by parents on demand. On the other hand, recurrence can cause sudden problems and pain, if intestines incarcerate. It is essential to treat recurrence before patients encounter acute incarceration with the risk of bowel gangrene, septicaemia and death. In girls an untreated recurrence can endanger mother and child during future pregnancy[142].

Recurrence may be detected by ultrasonography, chest X-ray, contrast-studies, MRI- or CT-scan. To address diaphragmatic complications another surgical intervention is needed, which may be prone to more complications due to adhesions.

[141] Waag et al. (2008); Tovar (2012); Morini and Bagolan (2012)
[142] Choi et al. (2021)

Incidences in literature vary between 4%[143] to 50%[144] - 57%[145] depending on patient selection, surgical procedure and patch material. Over decades still recurrence rates in up to 50% following patch repair were published[146]. Low recurrence rates in open surgery were reported after the use of a Gore-Tex®-patch (4%)[147] and after use of a dome-shaped patch (5.4%)[148].
A reduced recurrence rate of 9% after implantation of a cone-shaped patch was first published by Loff et al. in 2005[149].

After these promising preliminary results, a structured and standardized multidisciplinary longitudinal follow-up program was established at our institution to verify, whether this new implantation technique still proves to have a more favourable outcome in the long-term. Results are discussed in the context of internationally published data.

[143] Riehle et al. (2007)
[144] Moss et al. (2001)
[145] Rowe and Stolar (2003)
[146] Gasior and St Peter (2012)
[147] Riehle et al. (2007)
[148] Tsai et al. (2012)
[149] Loff et al. (2005)

2 MATERIAL AND METHODS

2.1 Methods

This study was approved by our local ethic committee and is in accordance to the Declaration of Helsinki[150]. I collected data prospectively from patients born between January 2003 and December 2012 until January 2016. This analysis concentrates on diaphragmatic complications depending on different surgical techniques. Most of our surviving patients are re-assessed regularly in our structured longitudinal follow-up-program, which includes interdisciplinary clinical, radiological, echocardiographic, pulmonary and neurodevelopmental investigation. After discharge from our hospital these children are evaluated at the age of 6, 12 and 24 months, 4, 6, 10 and 14-16 years.
A regular chest X-ray is performed at these intervals to look for diaphragmatic compications. At the age of two and ten years also a MRI-scan is conducted to investigate the diaphragm more accurately, visualize lung-perfusion in all patients and vascular status after ECMO therapy. If recurrence is suspected, also contrast-studies or CT-scans may be applied.

Since 2008 the size of the diaphragmatic defect was classified according to the CDH study group (figure 2, with friendly permission of Pam Lally)[151]:

In defect size A more than 90% of the affected hemidiaphragm are present and the defect usually lies 'intramuscular'. It is the smallest defect size. In defect size B 50%-75% of the hemidiaphragm are present and the defect involves less than 50% of the chest wall. In defect size C less than 50% of the hemi-diaphragm are present and more than 50% of the circumference of the chest wall are involved. Defect size D is the largest defect size and stands for complete or almost complete absence with less than 10% of the hemidiaphragm present.

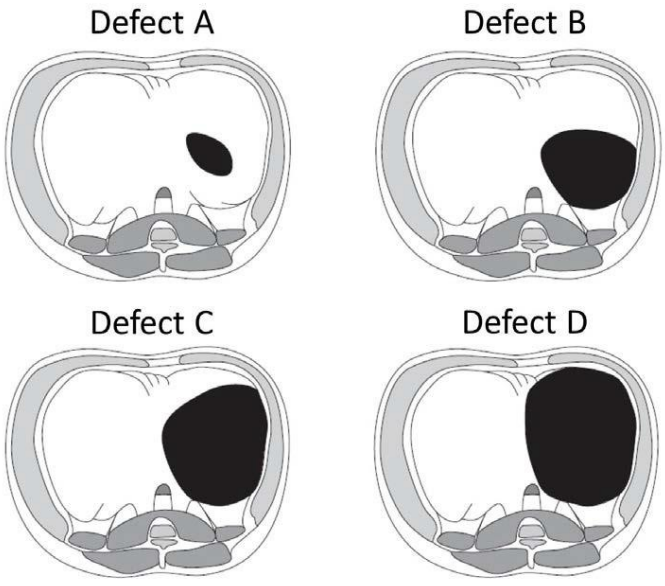


Figure 2: Classification of defect size in CDH according to the CDH study group (schematically shown for l-CDH)

[150] Bundesärztekammer (2013)
[151] Lally et al. (2013)

In our institution surgery is performed as delayed surgery after stabilization of the neonate. If ECMO therapy is required for sufficient stabilization, surgical correction of CDH is usually accomplished two days after termination of ECMO. Only rarely surgical correction is performed under ECMO therapy as a rescue manoeuvre, if there is no sufficient lung recruitment in patients with a large liver lobe herniated into the thoracic cavity.
Between 2003 and 2012 different surgical techniques have been used in open surgery via a median laparotomy: primary closure of the diaphragmatic defect, plane patch, 'oversize patch' and cone-shaped patch.

Primary repair was achieved in patients with sufficient diaphragm and smaller diaphragmatic defects by open surgery until 2007 and mainly by MIS since 2008. After mobilization of the diaphragmatic rim primary closure was achieved by multiple backstitch-sutures using non-absorbable suture material (Ethibond® 3-0). An example of open surgery in left-sided CDH is shown in figure 3.

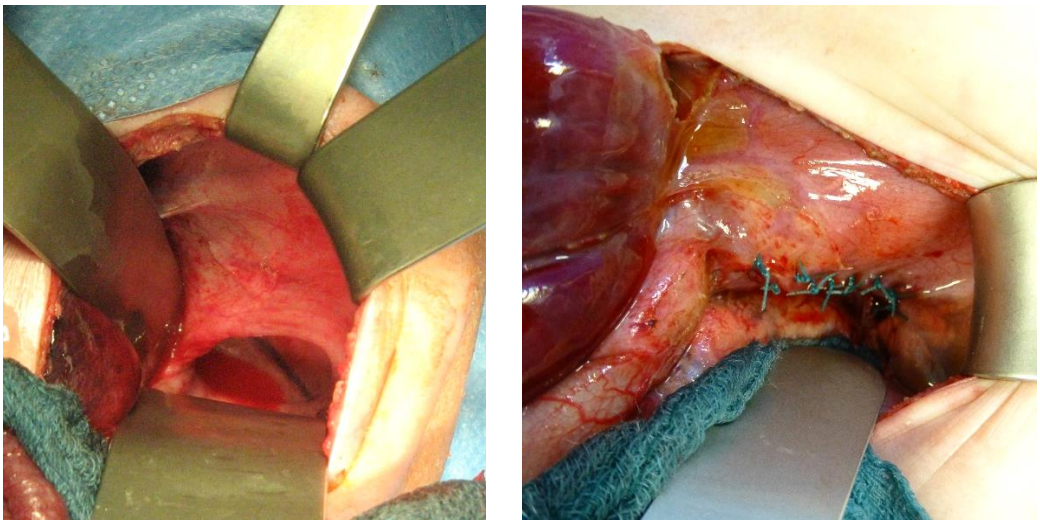


Figure 3: small diaphragmatic defect in left-sided CDH (defect size A according to CDH-SG) prior to (left) and after (right) primary closure

In larger defects a plane patch was cut to the size of the defect and directly sutured to the diaphragmatic border with multiple stitches. Non-absorbable material was used as patch and sutures. This is schematically shown in figure 4.

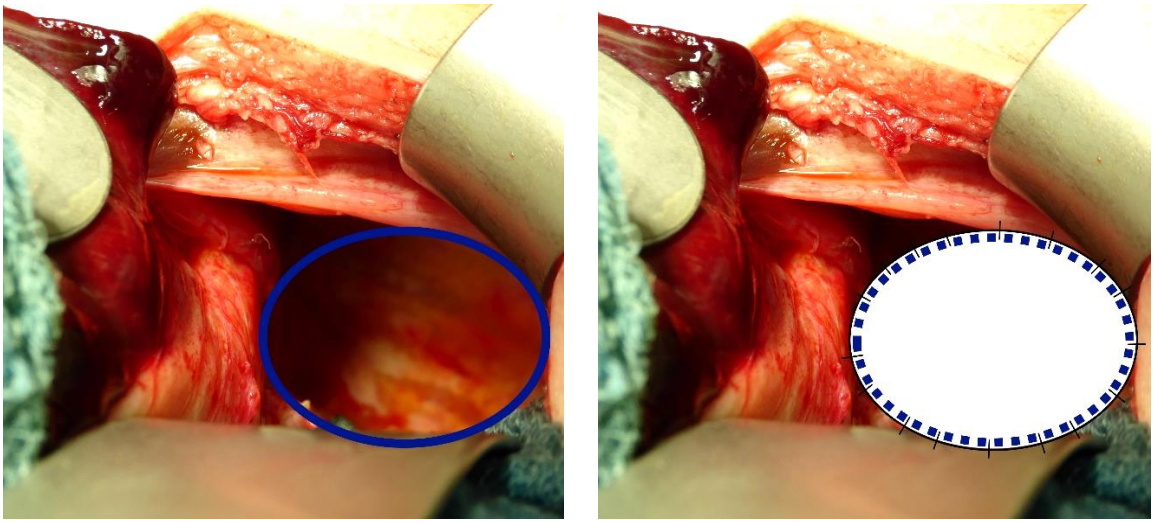


Figure 4: large diaphragmatic defect in left-sided CDH (defect size C according to CDH-SG) prior to (left) and after (right) closure with a plane patch

An 'oversized patch' has an overlapping edge, which is additionally sutured to the muscle and to the posterolateral abdominal wall in a second row of single stitches to enlarge the area of contact of synthetic material and surrounding tissue. Therefore patch-size exceeds defect size, which is schematically shown in figure 5.

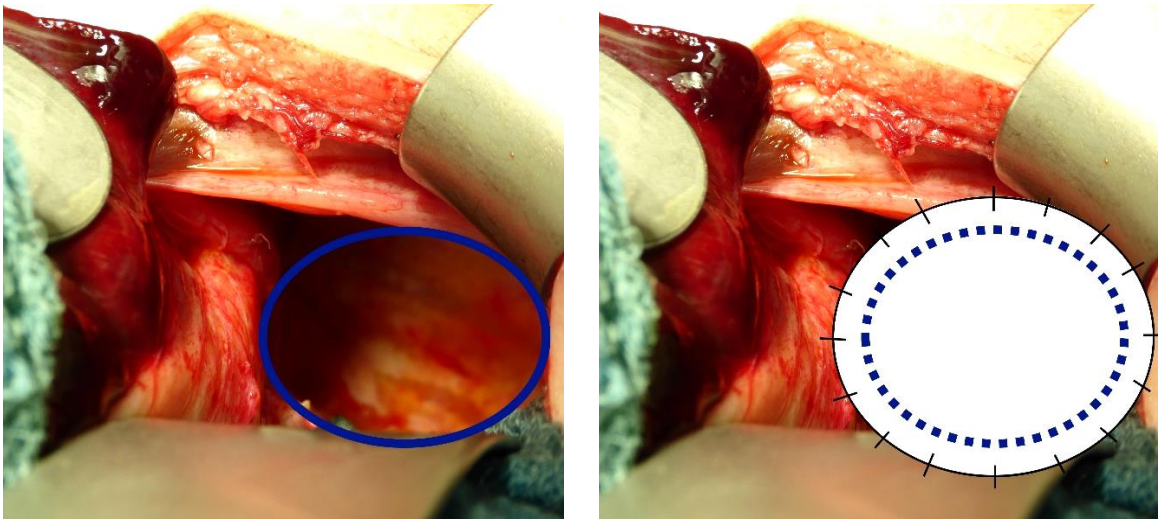


Figure 5: large diaphragmatic defect in left-sided CDH (defect size C according to CDH-SG) prior to (left) and after (right) closure with an ‚oversize'-patch

A cone-shaped patch has been used at our institution since 1999 and first results were published by Loff et al. in 2005[152].

Figure 6: cone-shaped patch after extracorporeal pre-formation

A Gore-Tex-Dualmesh® sheet is formed to a cone-shape extracorporeally and fixed with interrupted Ethibond® sutures (figure 6). For fixation to the diaphragm an overlapping suturing technique with pledget-sutures (Ticron®) is used. Pericostal Ethibond®-sutures are used posterolateral, where the diaphragm is absent. This patch is also sutured to the diaphragm and to the posterolateral abdominal wall with a second row of single stitches to create an overlapping border. With this technique patch-size also exceeds defect size, which is schematically shown in figure 7.

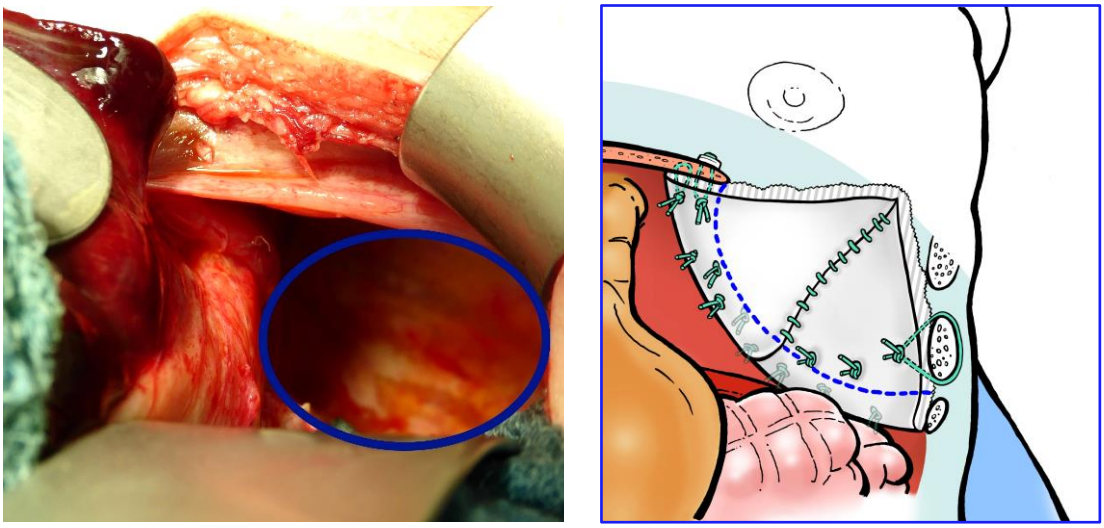


Figure 7: large diaphragmatic defect in left-sided CDH (defect size C according to CDH-SG) prior to (left) and after (right) closure with a cone-shaped patch

[152] Loff et al. (2005)

Furthermore, the patch protrudes towards the thoracic cavity and thus enlarges intraabdominal space while reducing intrathoracic volume - that is not filled out by the hypoplastic lung. Tension is reduced and on postoperative chest X-ray a physiologic contour of the diaphragm results after implantation of a cone-shaped patch. This is demonstrated in figure 8.

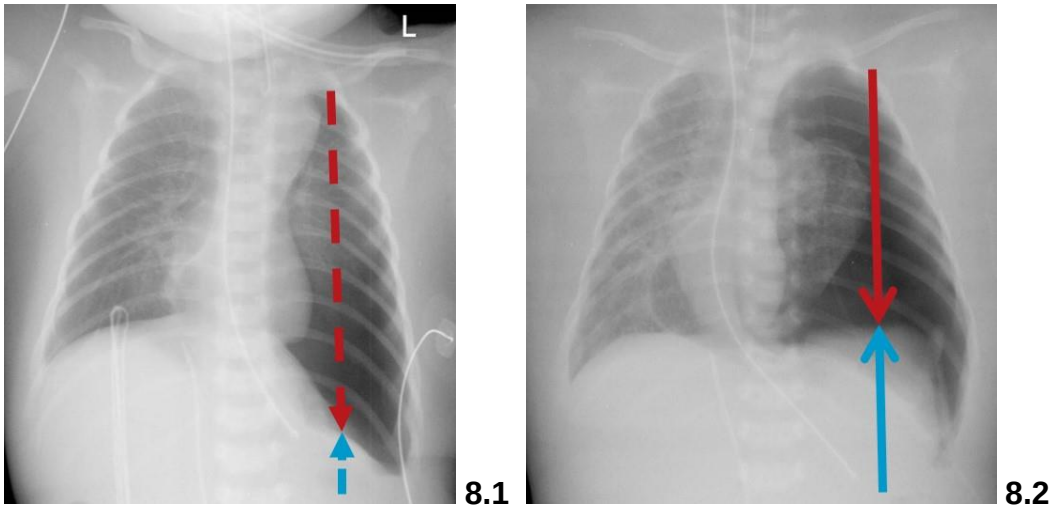


Figure 8: postoperative chest X-ray: intrathoracic volume indicated by red arrow, intraabdominal volume indicated by blue arrow; 8.1 after implantation of a plane patch; 8.2 after implantation of a cone-shaped patch (notice herniation of the left pleura to the right after repositioning a retrocardial spleen in a type D diaphragmatic defect)

2.2 Statistical analysis

For data analysis MedCalc Statistical Software version 15.8 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2015) was used. Fisher's exact test was used to test for statistical significance, because the number of expected frequencies was low. The level of significance is set at 0.05. Re-Recurrences were handled as separate recurrences in the data analysis. In multiple regression analysis recurrence was the dependent variable. Possible risk factors of recurrence were identified using Fisher's exact test and then entered into multiple regression analysis as independent variables. Afterwards relative risks and 95% confidence-intervals were calculated.

Rank correlation with Spearman's formula was used to test for the degree of relationship between recurrence and defect size, because the distribution of these two variables was not normal.

3 RESULTS

3.1 Epidemiologic data, mortality and follow-up

Between January 2003 and December 2012 508 neonates with congenital diaphragmatic hernia were treated at our institution (figure 9).

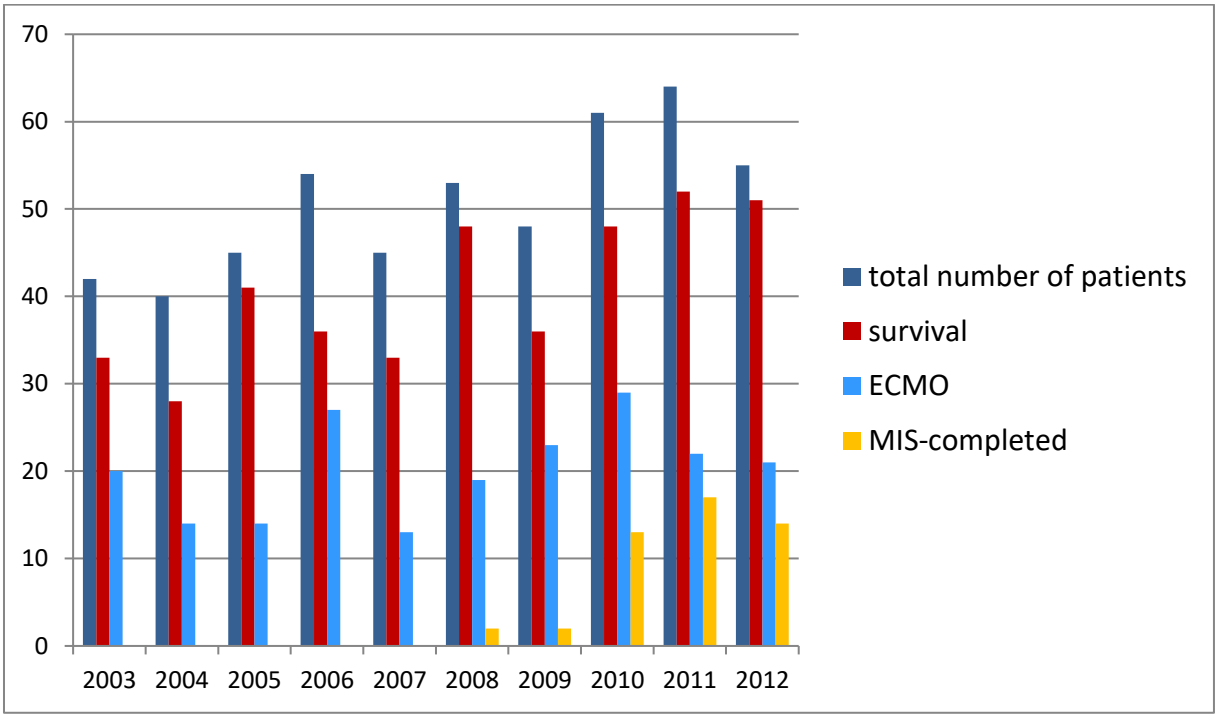


Figure 9: neonates with CDH born 01-2003 to 12-2012 at our institution: total number of patients, number of surviving patients, number of ECMO-patients and number of MIS-patients

In 400 patients (78.7%) the diagnosis was made antenatal, in 103 neonates (20.3%) after birth and in five children (1%) this data is missing. The median birth weight was 2900 g (885 g – 4890 g), median length at birth 49.5 cm (34 cm – 59 cm) and median gestational age 37+4 WOG (26+0 WOG – 42+0 WOG). ECMO-therapy was performed in 200 patients (39.4%) with a median duration of 10 days (1-22 days).

98 patients (19.3%) died within the first three months of life: 37 neonates (7.3%) deceased without surgical intervention due to prematurity, fatal syndrome, fatal associated congenital malformations, severe lung hypoplasia or contraindication to ECMO therapy. 29 of 200 ECMO-patients received ECMO therapy but did not survive to surgical correction of CDH (14.5%) and 26 children deceased after ECMO therapy and surgery for CDH (13%). Early mortality after ECMO therapy was overall 27.5% (55/200 ECMO-patients) and 15.2% in ECMO-patients who underwent CDH-repair after termination of ECMO therapy (26/171 operated ECMO-patients). Early mortality after surgery for CDH in nonECMO-patients was 2.2% (6/271 nonECMO-patients, including MIS-repair). This difference is statistically significant ($p<0.000001$).

In patients who underwent delayed surgical repair of CDH overall survival was 92.8%: 100% in patients after minimally invasive surgery (47/47 MIS-patients), 97.3% in open surgery without ECMO therapy (218/224 nonECMO-patients) and 84.8% in open surgery after ECMO therapy (145/171 ECMO-patients). In open surgery there was a significant difference in survival between nonECMO-patients compared to ECMO-patients (218/224 nonECMO-OS-patients versus 145/171 ECMO-OS-patients, p=0.000008). The difference in survival between MIS- and nonECMO-OS-patients was not significant (p=0.5942).

Since December 2008 defect size was documented in 181 patients according to the CDH-SG staging-system[153] (figure 2 and 10): defect size A in 22 patients (12.1%), defect size B in 54 patients (29.9%), defect size C in 89 patients (49.2%), defect size D in 16 patients (8.8%). Children with defect size A received primary closure in 100% and were operated by thoracoscopy in 81.8%. Patients with defect size B received a patch in 70.4%, 1/3 was operated by MIS. All patients with defect size C and D required patch implantation, 5.6% of patients with defect size C were operated thoracoscopically.

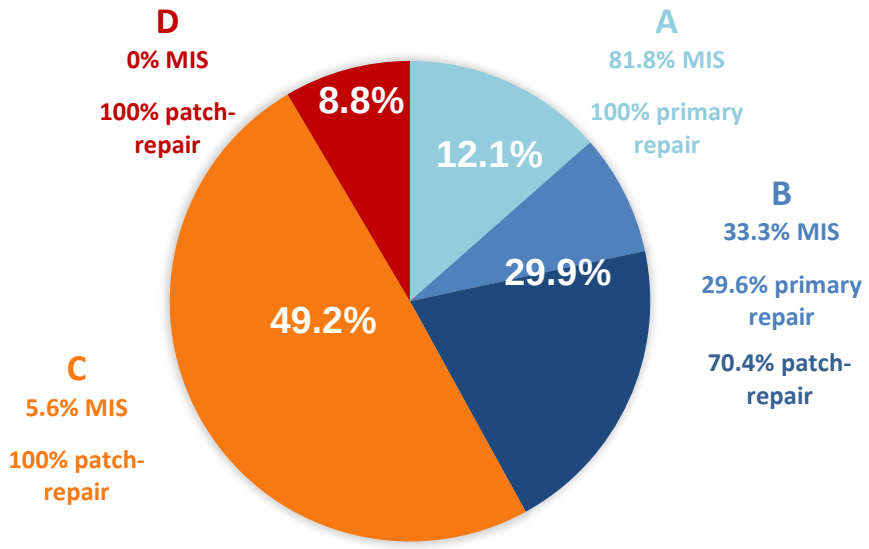


Figure 10: distribution of patients according to defect size (CDH-SG-staging system; 181 patients 2008-2012)

[153] Lally et al. (2013)

A consort diagram of the study cohort is presented in figure 11. Of 410 CDH-patients surviving to discharge 370 participated in our longitudinal follow-up program (90.2%). 47 MIS-patients were excluded from further analysis because the aim of the study was to evaluate diaphragmatic complications after open CDH-repair. In patients who were seen at an older age and did not have a recurrence, it was postulated that they also did not have one before this time. 326 patients with a minimum follow-up of two years were eligible for further analysis. Late mortality was not significantly higher in ECMO-patients (9/131 ECMO-patients (6.9%) versus 5/195 nonECMO-patients (2.6%), p=0.0916). The number of patients attending follow-up is shown in table 2.

*Table 2: age at follow-up investigation of surviving CDH-neonates, *14 late deaths*

age at follow-up	number of patients
≤ 2 years*	**326***
>2 ≤ 4 years	**224**
>4 ≤ 6 years	**154**
>6 ≤ 10 years	**57**

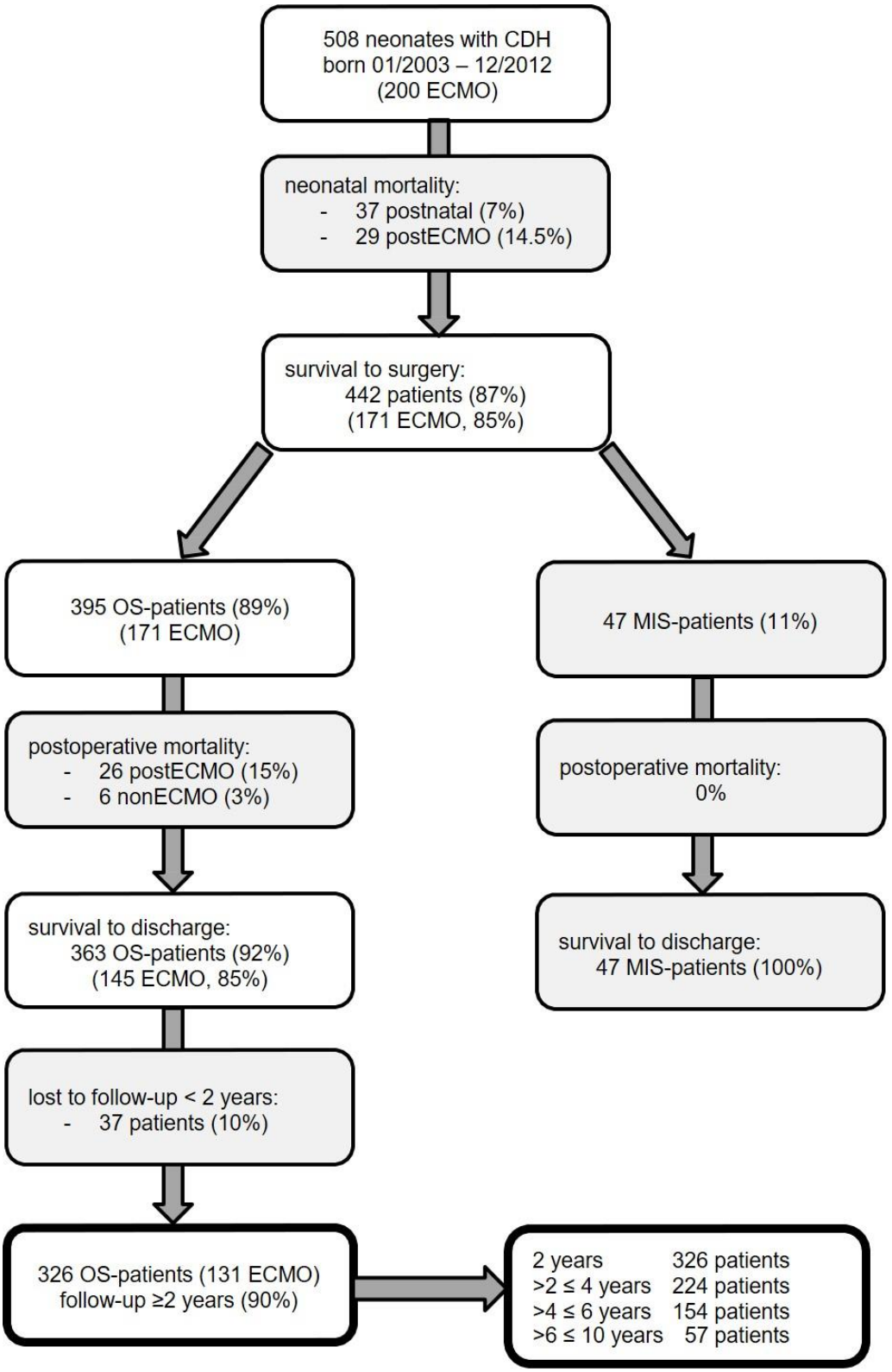


Figure 11: Neonates with congenital diaphragmatic hernia (CDH) born January 2003 to December 2012 at our institution and participation at follow-up until December 2015 with excluded patients in grey boxes (ECMO=extracorporeal membrane oxygenation, MIS=minimally invasive surgery, OS=open surgery)

3.2 Comparison of ECMO- and nonECMO-patients

Of 326 neonates, who survived to discharge and participated in our follow-up program so that longitudinal data is available, 131 (40.2%) received ECMO therapy. There was no difference in gender distribution, antenatal diagnosis, birth weight, length at birth and gestational age between ECMO- and nonECMO-patients. There was a significantly larger number of patients who underwent FETO in the ECMO-cohort (19/131 ECMO-patients versus 5/195 nonECMO-patients, p=0.0001). Right-sided CDH was predominant in ECMO-patients (29% versus 12.3% in nonECMO-patients, p=0.0003; table 3).

Table 3: comparison between ECMO- and nonECMO-patients after open surgery: epidemiologic data, prenatal therapy and late mortality (ECMO=extracorporeal membrane oxygenation; CDH=congenital diaphragmatic hernia; l=left-sided, r=right-sided; b=bilateral; FETO=fetoscopic endotracheal occlusion; WOG=weeks of gestation)

	Σ	**ECMO**	**nonECMO**	**p-value**
	n (%)	**n (%)**	**n (%)**	
patients	326 (100)	131 (40.2)	195 (59.8)	
gender	♂ 191 (58.6)	77 (58.8)	114 (58.5)	1.0
	♀ 135 (41.4)	54 (41.2)	81 (41.5)	
laterality of CDH	l 262 (82.2)	92 (70.2)	170 (87.2)	**0.0002**
	r 62 (17.2)	38 (29)	24 (12.3)	**0.0003**
	b 2 (0.6)	1 (0.8)	1 (0.5)	1.0
birth-weight median (range)	2980g (956g – 4890g)	2930g (1820g – 4890g)	3030g (956g – 4180g)	1.0
birth-length median (range)	50cm (35cm – 57cm)	50cm (40cm – 57cm)	50cm (35cm – 56cm)	1.0
gestational age median (range)	37+5 WOG (27+0 – 42+0)	37+4 WOG (33+1 – 42+0)	37+5 WOG (27+0 – 41+4)	1.0
prenatal diagnosis	260 (80.1)	104 (79.4)	156 (80)	0.9
FETO	24 (7.4)	19 (14.5)	5 (2.6)	**0.0001**
late mortality	14 (4.3)	9 (6.9)	5 (2.6)	0.09

In open surgery a ‘liver-up’-situation in left-sided CDH was found more often in the ECMO-group (82.6% versus 47.1% in nonECMO-patients, p<0.000001). An intrathoracic position of the stomach in left-sided CDH was also more frequent in ECMO-patients (89.1% versus 72.9% in nonECMO-patients, p<0.001). Defect size B was predominant in the nonECMO-group (28.1% versus 11.2% in ECMO-patients, p=0.008). On the other hand, defect size D was observed more often in the ECMO-group (18.7% versus 1% in nonECMO-patients, p=0.00003). Regarding defect size A there was no statistically significant difference, because the majority was operated by MIS in the nonECMO-group and therefore excluded from this analysis. The only patient with defect size A receiving ECMO-therapy was an outborn neonate with an antenatally not detected CDH, who developed severe pulmonary hypertension due to prolonged resuscitation. There was also no significant difference concerning defect size C in open surgery (52.5% in ECMO-patients versus 43.7% in nonECMO-patients, p=0.29) or concerning missing data regarding defect size between the two groups (16.2% in ECMO-patients versus 24% in nonECMO-patients, p=0.26).

In all ECMO-patients the diaphragmatic defect was repaired by open surgery, while 47 neonates underwent minimally-invasive surgery in the nonECMO-group (17.3%). The need for reconstruction of the diaphragm with a patch was 96.2% in ECMO-patients, while a primary repair was possible in 32.3% in the nonECMO-OS-cohort (p<0.000001). Also, the need for implantation of an abdominal wall patch to prevent abdominal compartment syndrome was significantly higher in ECMO-patients (32.8% versus 6.1% in nonECMO-OS-patients, p<0.000001). Concerning recurrence rate no difference between ECMO- and nonECMO-patients could be identified (table 4).

Table 4: comparison between ECMO- and nonECMO-patients after open surgery: intraoperative findings, type of surgery and overall recurrence (ECMO=extracorporeal membrane oxygenation; l-CDH=left-sided congenital diaphragmatic hernia; m.d.=missing data)

	Σ	**ECMO**	**nonECMO**	**p-value**
	n (%)	**n (%)**	**n (%)**	
patients	326 (100)	131 (40.2)	195 (59.8)	
liver-up in l-CDH	156 (59.5)	76 (82.6)	80 (47.1)	**<0.000001**
stomach-up in l-CDH	206 (78.6)	82 (89.1)	124 (72.9)	**<0.001**
primary repair	68 (20.9)	5 (3.8)	63 (32.3)	**<0.000001**
plane patch	2 (0.6)	0	2 (1)	0.52
'oversize' patch	5 (1.5)	1 (0.8)	4 (2)	0.65
cone-shaped patch	251 (77)	125 (95.4)	126 (64.6)	**<0.000001**
abdominal wall patch	55 (16.8)	43 (32.8)	12 (6.1)	**<0.000001**
defect size (since 2008, 140 pat.)	A 4 (2.9)	1 (1.5)	3 (4.1)	0.63
	B 36 (25.7)	9 (13.4)	27 (37)	**0.008**
	C 84 (60)	42 (62.7)	42 (57.5)	0.29
	D 16 (11.4)	15 (22.4)	1 (1.4)	**0.00003**
	m.d. 36 (20.4)	13 (16.2)	23 (24)	0.26
diaphragmatic complications	38 (11.7)	19 (14.5)	19 (9.7)	0.22

The incidence of ECMO therapy depending on laterality of CDH, position of liver and stomach in left-sided CDH, antenatal treatment, type of diaphragmatic reconstruction, type of abdominal closure and defect size is visualized in figure 12. ECMO-therapy for sufficient postnatal stabilization was necessary significantly more often in r-CDH (61% ECMO, p=0.0003) and in patients with an intrathoracic herniation of liver and stomach in l-CDH (liver-up: 48.7% ECMO, p<0.000001; stomach-up: 39.8% ECMO, p=0.0025). Children after antenatal FETO-therapy also received postnatal ECMO therapy significantly more often (79.2% ECMO, p=0.0001). Concerning surgical repair, ECMO-therapy was predominant in patients requiring diaphragmatic and abdominal wall patch (diaphragmatic patch: 50% ECMO, p<0.000001; abdominal wall patch: 78.2% ECMO, p<0.000001). Accordingly, patients with larger defect sizes required ECMO therapy significantly more often than patients with defect size A and B (defect C: 50% ECMO, p=0.0025; defect D: 94% ECMO, p=0.000002).

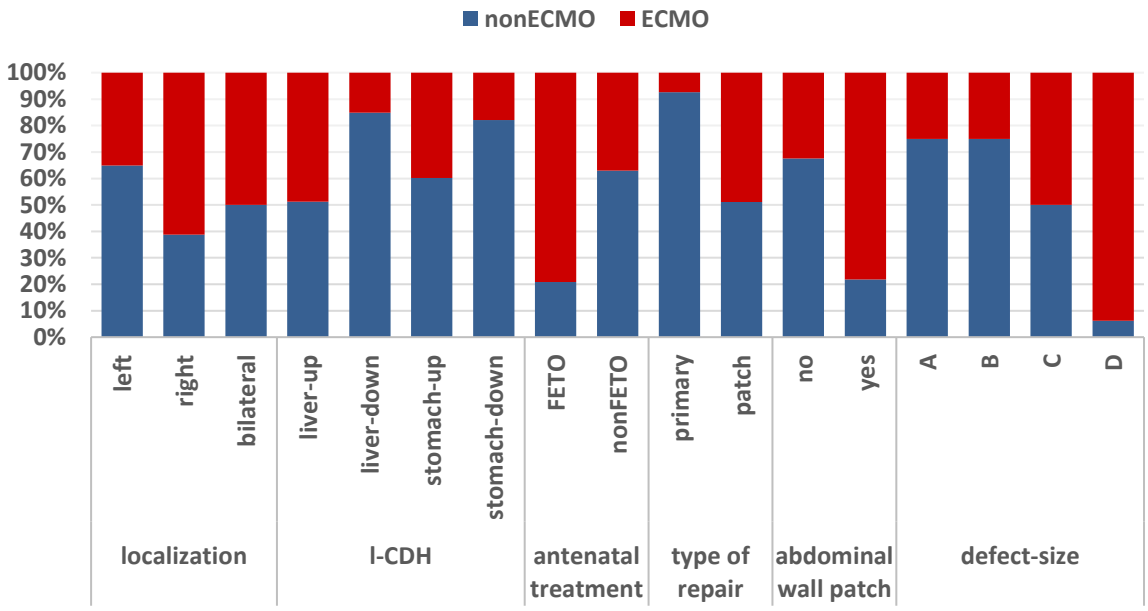


Figure 12: ratio of ECMO- and nonECMO-patients after open surgery: depending on laterality of CDH, position of liver and stomach in left-sided CDH, antenatal treatment, type of diaphragmatic reconstruction, type of abdominal closure and defect size (ECMO=extracorporeal membrane oxygenation; l-CDH=left-sided congenital diaphragmatic hernia; FETO=fetoscopic endotracheal occlusion)

3.3 Diaphragmatic complications in open surgery

There were 38 diaphragmatic complications detected in 31 patients (9.5%) within an observational time of a minimum of two years to a maximum of ten years in open surgery. In five patients two recurrences and in one patient with Cornelia-di-Lange-syndrome three recurrences were observed. For further analysis, each of the re-recurrences was handled as a separate one. There was no statistically significant difference in diaphragmatic complications regarding gender (26R/170nonR in 191 male patients versus 12R/125nonR in 135 female patients, p=0.22).

We have detected two different types of diaphragmatic complications: on the one hand 'true' recurrence at the localization of the original diaphragmatic defect and on the other hand secondary hiatal hernia (figure 13 and 14). 'True' recurrence after patch implantation can be due to pericostal sutures growing through the ribs with time (dorsolateral recurrence) or a distraction of the patch from the hypoplastic medio-dorsal diaphragmatic rim. Secondary hiatal hernia after patch implantation is caused by distraction of the diaphragmatic crura from the oesophagus especially in patients with only a hypoplastic medial diaphragmatic rim and initial intrathoracic herniation of the stomach.
Of our 38 diaphragmatic complications 24 were 'true' recurrences (63%) and eight hiatal hernias (21%), while in six cases both types co-occurred (16%).

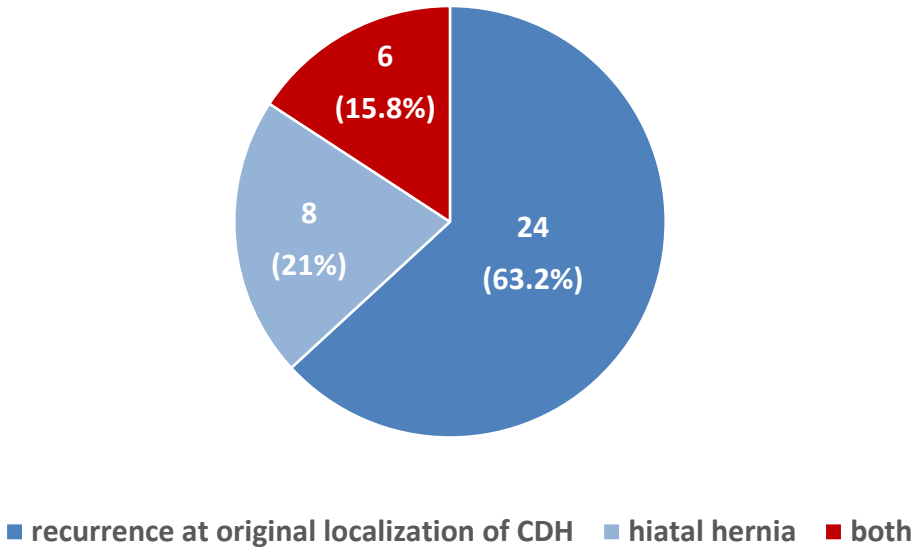


Figure 13: diaphragmatic complications: prevalence of recurrence at the original localization of congenital diaphragmatic hernia (CDH), secondary hiatal hernia and co-occurrence

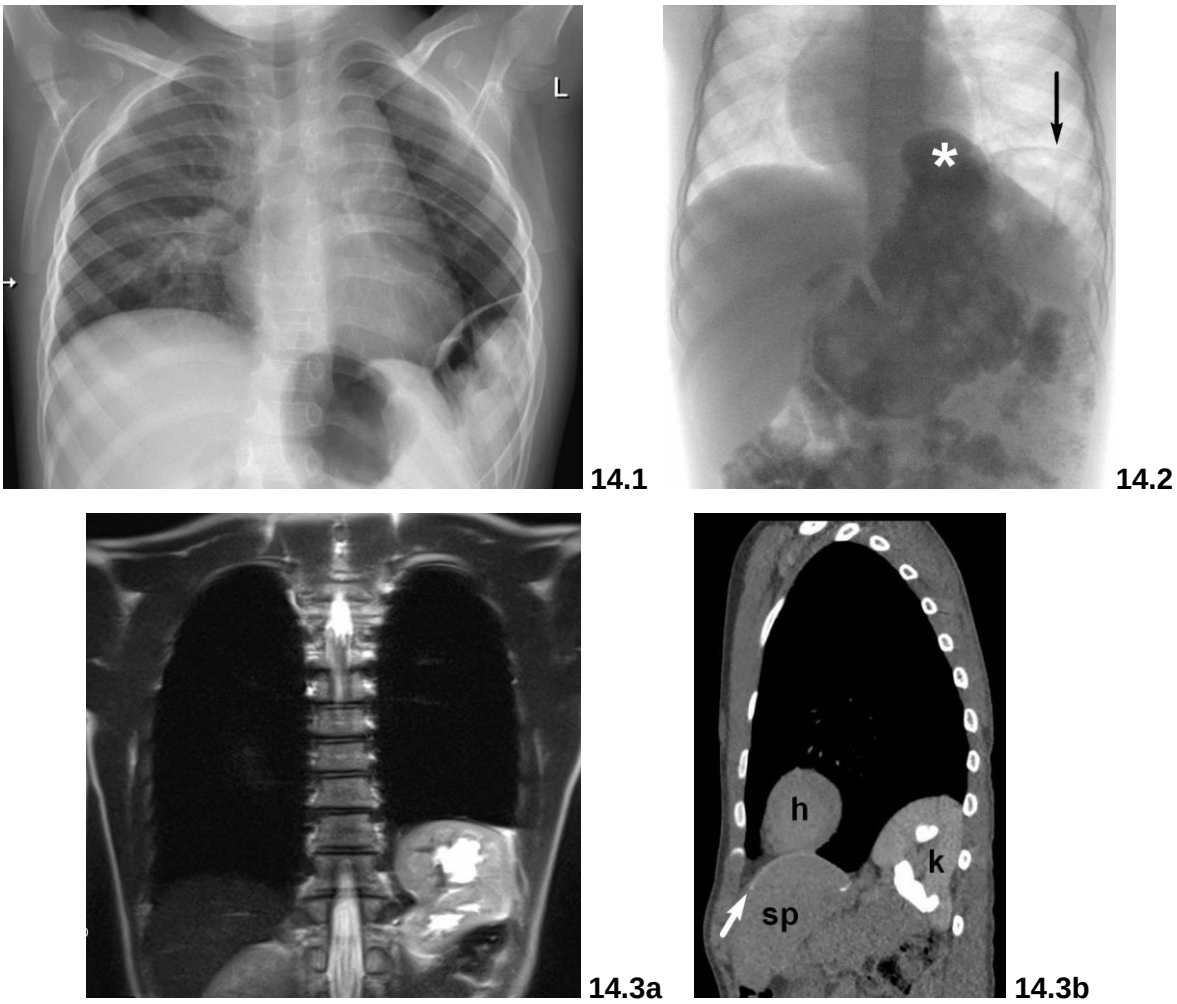


Figure 14: radiological diagnosis of diaphragmatic complications (14.1 plane chest X-ray in a 2-year-old boy: lateral recurrence; 14.2 contrast-study in a 4-year-old boy: hiatal hernia (*) and lateral recurrence (→); 14.3 MRI (a) and lowdoseCT (b) in a 10-year-old girl with thoracic herniation of the left kidney (CT-scan (b): h=heart, k=kidney, sp=spleen, cone-shaped patch marked with white arrow))

Patient characteristics regarding different diaphragmatic complications are summarized in table 5.

In all patients with **secondary hiatal hernia** (isolated and combined with a 'true' recurrence) a left-sided CDH was present and the stomach was located intrathoracically during the initial operation. An intrathoracic position of the left liver-lobe was noted in 64% of patients. A cone-shaped patch was implanted in six of eight patients (75%) with isolated hiatal hernia, while a primary repair was achieved in two (25%). None of these patients required ECMO-therapy. Six of eight patients with an isolated hiatal hernia were asymptomatic (75%), whereas two presented problems with gastro-esophageal reflux (25%). Four patients were treated with a secondary hiatoplasty and fundoplication (50%). Four asymptomatic patients are under observation and have not undergone another surgical intervention.

Five of six patients with a **co-ocurrence** of 'true' CDH-recurrence and secondary hiatal hernia required ECMO-therapy (83.3%) and half of the patients an abdominal wall patch. Diaphragmatic reconstruction was performed using a cone-shaped patch in five patients (83.3%), while a primary repair was achieved in one (16.7%). All patients showed mild symptoms at the time of diagnosis (tachypnea (16.7%), gastro-esophageal reflux (50%), constipation (33.3%)). All patients underwent secondary surgery with hiatoplasty and fundoplication for hiatal hernia and correction of 'true' recurrence either by re-fixation of the primary patch or an overlapping second patch after primary patch-repair (figure 15). In one patient after initial primary repair primary closure of the recurrent defect was again achieved.

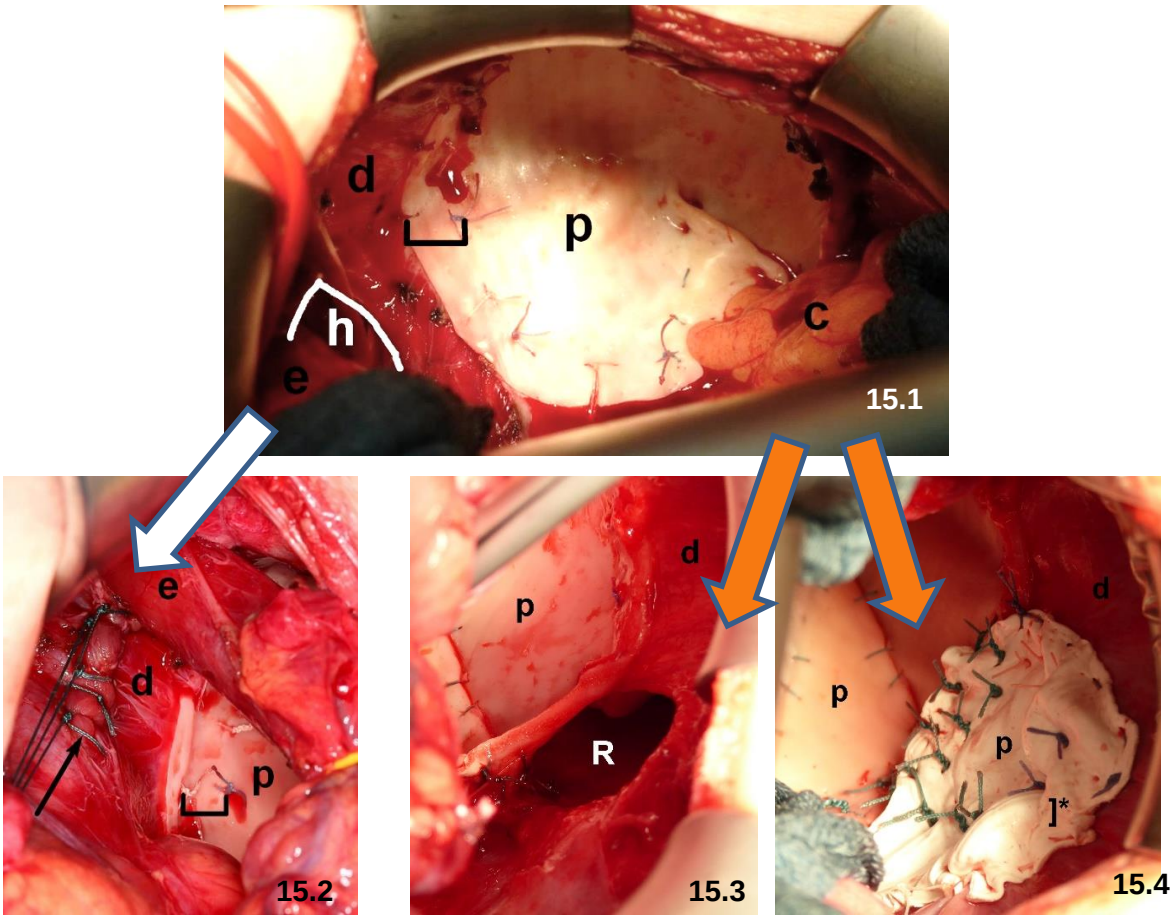


Figure 15: intraoperative situation in co-occurrence of 'true' CDH-recurrence and secondary hiatal hernia in a 4-year-old boy after implantation of a cone-shaped Goretex®-patch: 15.1 d=diaphragm, h=hiatal hernia, e=esophagus,]=overlapping border, p=patch, c=colon; 15.2 closure of hiatal hernia with posterior hiatoplasty (marked with black arrow), 15.3 lateral recurrence (R), 15.4 closure of lateral CDH-recurrence with second Goretex-Dualmesh®-patch and fixation to diaphragm and abdominal wall with overlapping border ( ])*

14 of 24 patients with **'true' recurrence** received ECMO-therapy (58.3%). Most patients with left-sided CDH and 'true' recurrence had an intrathoracic position of liver (87%) and stomach (87%). Reconstruction of the diaphragm was achieved by implantation of a patch in 21 of 24 patients (87.5%). An abdominal wall patch was required in 11 of 24 OS-patients (45.8%). 23 patients underwent secondary surgery: primary repair in three patients (12.5%), patch implantation after primary repair in the first operation in one patient (4.2%), re-fixation of the primary patch in three children (12.5%) and an overlapping second patch in 14 patients (58.3%). Five children underwent secondary surgery at another hospital (20.8%) and in two the type of repair is not known (8.3%). In one asymptomatic patient parents refused to give their consent to another surgery (4.2%). Of all patients with 'true' recurrence 10 were asymptomatic (41.7%), four showed respiratory symptoms (16.7%), four GER (16.7%) and five constipation or feeding problems (20.8%). Thus, in this cohort 23 patients (95.8%) showed either no or minor symptoms of recurrence. Only one patient (4.2%) presented with acute signs of incarceration and bowel obstruction. This patient had a left-sided CDH, no ECMO-therapy, patch-repair and developed recurrence below six months of age.

Table 5: Patient-characteristics concerning diaphragmatic complications: epidemiologic data, intraoperative findings and type of surgery, symptoms and recurrence repair rate (l-CDH=left-sided congenital diaphragmatic hernia; r-CDH=right-sided congenital diaphragmatic hernia; ECMO=extracorporeal membrane oxygenation)

	'true' recurrence (n=24)	**hiatal hernia (n=8)**	**co-occurrence (n=6)**
	n (%)	**n (%)**	**n (%)**
l-CDH	23 (96)	8 (100)	6 (100)
r-CDH	1 (4)	0	0
liver-up in l-CDH	20 (87)	5 (63)	4 (67)
stomach-up in l-CDH	20 (87)	8 (100)	6 (100)
ECMO	14 (58)	0	5 (83)
primary repair	3 (12)	2 (25)	1 (17)
cone-shaped patch	21 (88)	6 (75)	5 (83)
abdominal wall patch	11 (46)	1 (12)	3 (50)
symptoms	14 (58)	2 (25)	6 (100)
surgical repair	24 (100)	4 (50)	6 (100)

3.3.1 Time

Early recurrence

In three of 410 patients surviving to discharge (0.7%) recurrence occurred during the first hospital stay.

Late diaphragmatic complications

After discharge, 18 diaphragmatic complications of CDH were diagnosed within the first year of life (51.4%) and 11 (31.4%) within the second. In three patients these were detected between two and four years of age (8.6%) and in another three patients between four and 10 years of age (8.6%). Thus, the incidence of diaphragmatic complications was highest within the first 12 months of life (21/326 patients, 6.4%) and reduced to about half in the second year of life (11/326 patients, 3.4%). In patients between two and four years of age the incidence was 1.3% (3/224 patients) and 1.9% in children older than four years (3/154 patients), respectively.

One patient below six months of age presented with acute signs of incarceration and intestinal obstruction (2.6%). In 35 patients (92.1%) diaphragmatic complications were detected or at least suspected on native chest-X-ray before discharge or on follow-up visits. Additional imaging with CT, MRI or contrast study was performed in cases of doubt to confirm or rule out the diagnosis (examples in figure 14). In two patients (5.3%) undergoing re-laparotomy (one for fundoplication and one for adhesive small bowel obstruction) a developing recurrence laterally was detected and also repaired. The majority of children was either asymptomatic (16/37 patients, 43.2%) or showed at least one of the following mild and nonspecific symptoms: intermittent abdominal pain (14/37, 37.8%), gastroesophageal reflux (GER; 9/37 patients, 24.3%), a change in eating habits and stooling frequency (7/37 patients, 18.9%), tachypnea (n=5/37 patients, 13.5%). Weight at follow-up visits was not obtained routinely in the beginning of the follow-up program. Nevertheless, in those children with available data weight of recurrence-patients was below the median weight of non-recurrence-patients at follow-up visits in 66.2% (47/71 recurrence-patients), see table 6.

Table 6: Comparison of patients with (R) and without (nonR) diaphragmatic complications concerning weight at follow-up visits (GA=gestational age)

follow-up visit	nonR-patients GA: median 37+5 (min. 27+0, max. 42+0)			R-patients GA: median 37+3 (min. 32+1, max. 40+2)			
	n	median weight in kg	range (min-max) in kg	n	median weight in kg	range (min-max) in kg	weight below median of nonR-patients n (%)
1 year	218	7.9	4.4-12.5	23	7.3	4.83-10	15 (65.2)
2 years	219	10.8	6.4-15.5	23	10	5.8-13.4	16 (69.6)
4 years	129	14	8.7-20	14	13.1	8.2-19	9 (64.3)
6 years	97	18	12.8-26	7	15.5	10.6-18	6 (85.7)
10 years	24	26.25	19.1-41.8	4	28.3	23.8-32	1 (25)

3.3.2 Laterality of CDH

Only one recurrence was observed in 62 patients with right-sided CDH (1.6%), while 37 recurrences were detected in 262 survivors with left-sided CDH (14.1%, p=0.0036). In left-sided CDH, patients with diaphragmatic complications had a significantly higher rate of intrathoracic herniation of liver and stomach (29R/130nonR in 156 ‘liver-up’-patients versus 8R/102nonR in 106 ‘liver-down’-patients, p=0.01; 34R/178nonR in 206 ‘stomach-up’-patients versus 3R/51nonR in 53 ‘stomach-down’-patients, p=0.049).

3.3.3 ECMO-therapy

One or more recurrences were observed in 17 of 131 surviving ECMO-patients (13%) and 14 of 195 surviving nonECMO-patients (7.2%). This difference was not statistically significant (p=0.09). Overall 19 diaphragmatic complications (R) were observed in the ECMO- as well as in the nonECMO-group (19R/114nonR in 131 ECMO-patients versus 19R/181nonR in 195 nonECMO-patients, p=0.22).

3.3.4 Defect size

In open surgery, there was a significant correlation with defect size in 140 patients, in whom the diaphragmatic defect was intraoperatively classified according to the CDH-SG: the larger the initial defect, the higher is the risk for recurrence (correlation coefficient r=0.26; p=0.0017; 95% confidence interval for r 0.100-0.408). In defect size A recurrence rate was 0%, in defect

size B 2.8%, in defect size C 13.1% and in defect size D 37.5% (figure 16). The difference between small and large diaphragmatic defects was statistically significant (1R/39nonR in 40 patients with defect size A+B versus 17R/86nonR in 100 patients with defect size C+D, p=0.02). There was a tendency towards a higher recurrence rate in defect size D compared to defect size C (11R/73nonR in 84 patients with defect size C versus 6R/13nonR in 16 patients with defect size D, p=0.08).

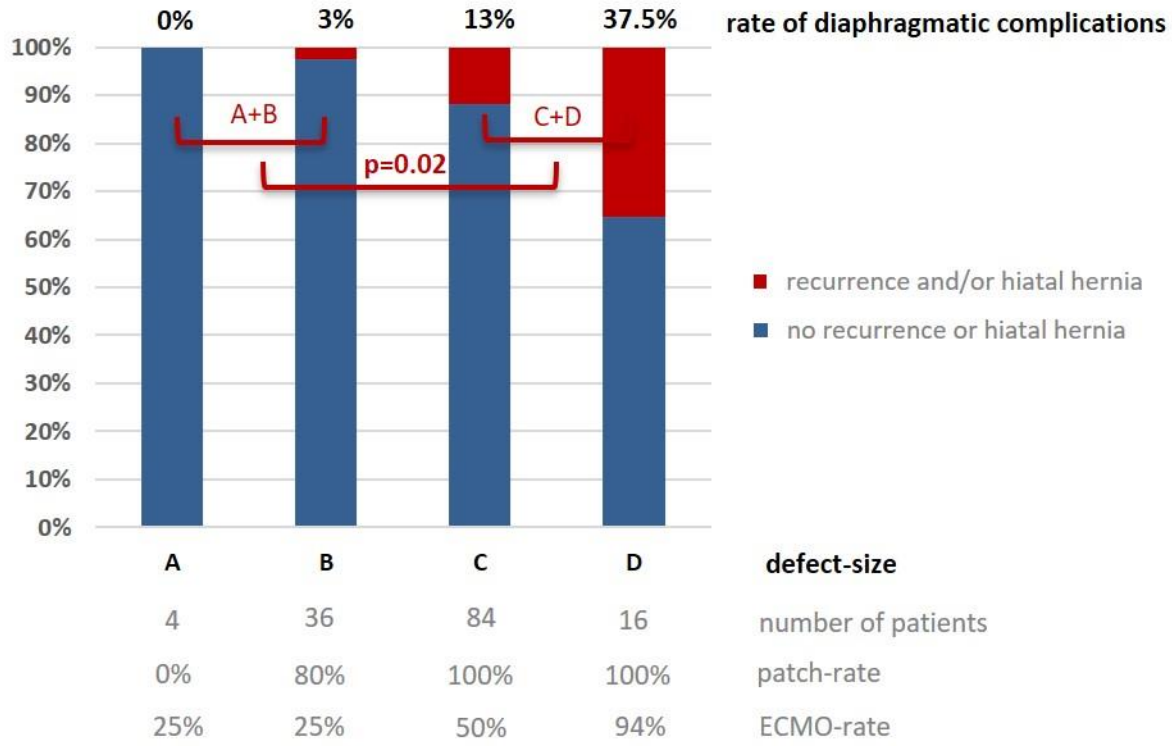


Figure 16: rate of recurrence and/or secondary hiatal hernia in relation to defect size A-D[30] in 140 patients after open surgery 2008-2012: the larger the defect size the higher is the complication rate, significant difference between small and large defects (1/40 A+B versus 17/100 C+D; p=0.02), additionally patch- and ECMO-rate depending on defect size are displayed (ECMO=extracorporeal membrane oxygenation)

3.3.5 Type of CDH-repair

Even though a significantly higher rate of diaphragmatic complications was detected in larger CDH-defects, there was no significant difference regarding the type of diaphragmatic reconstruction (6R/64nonR in 68 patients with primary repair versus 32R/224nonR in 251 patients with cone-shaped-patch, p=0.53). Only 7 of 258 patch-patients (2.7%) received other patch-types (2 plane patch, 5 oversize-patch) and in none of those recurrence was observed. Before, higher recurrence rates within the first year had been observed after implantation of plane and oversized patches and published by our group (plane patch: 46% recurrence,

'oversize-patch': 11% recurrence, cone-shaped patch: 9% recurrence)[154]. Therefore, there was a change in the surgical approach for diaphragmatic reconstruction towards using a cone-shaped patch in our institution.

3.3.6 Patch material

In this cohort solely non-absorbable material was used for patch implantation (Goretex-Dualmesh®) and as sutures (Ethibond®, Ticron®) and therefore no differentiation of absorbable and non-absorbable material concerning recurrence rate can be made.

3.3.7 Type of abdominal closure

There was a significantly higher risk of recurrence after implantation of an abdominal wall patch (15R/41nonR in 55 patients with abdominal wall patch versus 23R/254nonR in 271 patients without abdominal wall patch, p=0.0003).

In our cohort the abdominal wall patch clearly reflects disease severity: of 55 patients that required implantation of an abdominal wall patch 54 also required a patch for diaphragmatic reconstruction (98%) - only in one patient with associated omphalocele diaphragmatic closure was achieved by primary repair. 78% of patients required ECMO-therapy for sufficient postnatal stabilization and 11% had undergone prenatal FETO-therapy. In left-sided CDH an intrathoracic position of the liver was detected in 89% and of the stomach in 98%. Defect size according to the CDH-study group was classified in 44 patients and large defect sizes were predominant (A: 0%, B: 7%, C: 66%, D: 27%). Compared to patients without abdominal wall patch the difference of these parameters is highly significant (table 7).

[154] Loff et al. (2005)

Table 7: comparison between patients with and without abdominal wall patch: intraoperative findings and type of surgery (one patient with associated omphalocele; CDH=congenital diaphragmatic hernia; FETO=fetoscopic endotracheal occlusion; ECMO=extracorporeal membrane oxygenation)*

		abdominal wall patch (n=55*)	no abdominal wall patch nonR (n=271)	p-value
		n (%)	n (%)	
l-CDH		47* (86)	215 (79)	0.26
r-CDH		7 (13)	55 (2)	
liver-up in l-CDH		42* (89)	114 (53)	**0.000002**
stomach-up in l-CDH		46 (98)	160 (74)	**0.0001**
FETO		6 (11)	18 (7)	0.26
ECMO		43 (78)	88 (32)	**<0.000001**
primary repair		1* (2)	67 (25)	**<0.00002**
cone-shaped patch		54 (98)	204 (75)	
defect-size[30] (since 2008, 140 pat.)	A	0 (0)	4 (4)	0.31
	B	3* (7)	33 (34)	**0.0003**
	C	29 (66)	55 (57)	0.36
	D	12 (27)	4 (4)	**<0.0002**

3.4 Comparison of patients with and without diaphragmatic complications

Significant differences between patients with and without diaphragmatic complications could be identified concerning 1. laterality of the diaphragmatic defect ($p<0.02$), 2. an intrathoracic herniation of the left liver-lobe in left-sided CDH ($p=0.001$) and 3. the implantation of an abdominal wall patch ($p=0.00006$). The difference concerning an intrathoracic stomach-position in left-sided CDH also reached significance ($p=0.05$). A tendency to a higher incidence of larger defects in patients with recurrence could be detected (defect size A+B / C+D: 1/14 R-patients versus 39/86 nonR-patients, $p=0.067$).

No significant differences between R- and nonR-patients could be detected concerning antenatal FETO-therapy ($p=0.49$), ECMO-therapy ($p=0.086$) and type of diaphragmatic repair ($p=0.35$). Concerning initial defect size of CDH there was a significantly lower number of patients with defect size B and a significantly higher number of patients with defect size D in the R-cohort (A: $p=1.0$; B: $p=0.04$; C: $p=1.0$; D: $p=0.02$). These results are displayed in table 8.

3.5 Multivariate analysis for risk factors

In multiple regression analysis the risk factors identified by Fisher's exact test were analyzed to verify, if they were influencing diaphragmatic complications independently. In all patients CDH-laterality and the need for an abdominal wall patch were independent variables for diaphragmatic complications (multiple correlation coefficient 0.31, CDH-laterality $p=0.03$; abdominal wall patch $p<0.001$, F-ratio 17, $p<0.001$).

In l-CDH an abdominal wall patch was an independent variable, while liver- and stomach-position were not (multiple correlation coefficient 0.34, 'liver-up' $p=0.07$; 'stomach-up' $p=0.53$; abdominal wall patch $p<0.001$, F-ratio 11.5, $p<0.001$).

In patients with classification of the size of the diaphragmatic defect (n=140) the necessity for an abdominal wall patch was an independent variable ($p=0.0002$), while defect size D did not matter ($p=0.1713$). Laterality of CDH did not have a significant effect in this cohort, because the only patient with recurrence in r-CDH was born before 2008 and defect size was therefore not classified.

Table 8: comparison between patients with (R) and without (nonR) diaphragmatic complications: epidemiologic data, intraoperative findings and type of surgery (l-CDH=left-sided congenital diaphragmatic hernia; r-CDH=right-sided congenital diaphragmatic hernia; FETO=fetoscopic endotracheal occlusion; ECMO=extracorporeal membrane oxygenation)

		R (n=38)	nonR (n=295)	p-value
		n (%)	n (%)	
male		26 (68)	170 (58)	0.22
female		12 (32)	125 (42)	
l-CDH		37 (97)	232 (79)	**<0.004**
r-CDH		1 (3)	61 (21)	
liver-up in l-CDH		29 (78)	130 (56)	**0.01**
stomach-up in l-CDH		34 (92)	178 (77)	**0.049**
FETO		5 (13)	21 (7)	0.2
ECMO		19 (50)	114 (39)	0.22
primary repair		6 (16)	64 (22)	0.53
cone-shaped patch		32 (84)	224 (76)	
abdominal wall patch		15 (40)	41 (14)	**0.0003**
defect-size[30] (since 2008, 140 pat.)	A	0	4 (3)	1.0
	B	1 (6)	35 (28)	**0.04**
	C	11 (61)	73 (58)	1.0
	D	6 (33)	13 (10)	**0.02**

3.6 Determination of relative risks

Accordingly, the relative risk for diaphragmatic complications was significantly increased to 8.5 in left-sided CDH (p=0.03) and to 3.2 in patients requiring the implantation of an abdominal wall patch (p=0.0001). In l-CDH the relative risk was 2.5-fold higher in neonates with an intrathoracic position of the liver (p=0.01) and 2.9-fold higher with an intrathoracic herniation of the stomach, although this was not statistically significant (p=0.069). Patients with larger defect sizes (C+D) had a 6.6-fold higher relative risk to develop problems than patients with smaller defect sizes (A+B), although this did not quite reach statistical significance (p=0.06). But in patients with defect size D the risk was significantly increased to 2.4 in comparison to children with defect size C (p=0.04).

A significantly increased relative risk could also be calculated concerning the time of diagnosis: it was increased to 3.9 in children younger than or equal to two years as compared to older children (p<0.002). Patients even had a 6.5-fold higher risk for diaphragmatic complications within the first four years of life as compared to older age (p<0.002). Also, the relative risk was increased significantly within the first two years of life as compared to children aged two to four years (RR 7.6, p=0.0007). The relative risks for different risk factors are summarized in table 9.

Table 9: risk factors for diaphragmatic complications after neonatal CDH-repair and increased relative risks (RR=relative risk; 95% CI=95% confidence interval; l-DH=left-sided congenital diaphragmatic hernia)

risk-factor	RR	95% CI	p-value
abdominal wall patch	**3.2**	**1.8-5.8**	**0.0001**
l-CDH	**8.5**	**1.2-61.0**	**0.0327**
'liver-up' in l-CDH	**2.5**	**1.2-5.3**	**0.0154**
'stomach-up' in l-CDH	2.9	0.9-9.0	0.0688
defect size C+D/A+B	6.6	0.9-48.0	0.0622
defect size D/C	**2.4**	**1.0-5.7**	**0.0451**
age ≤ 2 years / 2≤4 years	**7.6**	**2.4-24.6**	**0.0007**
age ≤ 2 years / >2 years	**3.9**	**1.6-9.1**	**0.0019**
age ≤ 4 years />4 years	**6.5**	**2.0-20.7**	**0.0017**

4 DISCUSSION

This study demonstrated that longitudinal follow-up with regular radiologic investigation allows a reliable detection of diaphragmatic complications with the vast majority of these patients showing no or nonspecific symptoms and about half occurring beyond one year of age. To our knowledge, it has not been described before that not only recurrence at the localization of the original diaphragmatic defect but also secondary hiatal hernia is a common complication after neonatal CDH-repair. Furthermore, patients with large defects are prone to develop both. In this study-cohort with a predominance of large CDH a low rate of diaphragmatic complications might have been achieved with the implantation of a broad cone-shaped, non-absorbable patch. As independent risk factors left-sided CDH and the necessity for an abdominal wall patch could be identified in multivariate analysis.

Reports on late recurrences after open surgery vary strikingly between 4%[155] and 57%[156] and seem to depend on technique of diaphragmatic reconstruction and material of patch. No decline in recurrence over decades can be noticed with a recurrence rate in up to 50% following patch-repair with non-absorbable material being published by Gasior[157] in 2012. Multiple factors can influence recurrence in open surgery: type of diaphragmatic repair, patch material, implantation technique and various patient-characteristics. These will be further elucidated and the results of this largest single-centre cohort so far will be discussed in the context of internationally published data. Yet, it is difficult to compare studies due to different approaches to detect recurrence. Most studies are retrospective and did not offer long-term follow-up – if any – to all surviving CDH-patients. Also, follow-up did not regularly comprise radiologic imaging. Therefore, recurrence rates published in these studies are certainly underestimated. Only a structured follow-up with regular radiologic investigation allows a reliable detection of recurrence. If we had performed radiologic imaging only in apparently symptomatic patients, we would have diagnosed just 2.6% of recurrences in our cohort.

4.1 Diaphragmatic complications in open surgery

No study investigating ‘true’ recurrence and secondary hiatal hernia has been reported so far. ‘True’ recurrence after patch implantation can be due to pericostal sutures growing through the ribs or distraction of the patch from the hypoplastic diaphragm. In our cohort it was observed much more often (7.4%) than hiatal hernia (2.5%) or co-occurrence (1.8%; figure 13). Patients with ‘true’ recurrence had larger diaphragmatic defects with intrathoracic position of liver and stomach (87%), higher incidence of ECMO-therapy (58.3%), diaphragmatic patch-repair

[155] Riehle et al. (2007)
[156] Rowe and Stolar (2003)
[157] Gasior and St Peter (2012)

(87.5%) and implantation of an abdominal wall patch (45.8%). In most patients recurrence was repaired with an overlapping second patch (58.3%). ‚True' recurrence bears the risk of intestinal complications such as chronic gastrointestinal problems possibly resulting in failure to thrive with its potential negative impact on neurologic and cognitive development[158]. On the other hand, acute incarceration with the risk of bowel gangrene and lethal septicaemia can result[159]. This can also happen after decades in undiagnosed CDH, attributing to a high risk of complications with associated mortality and morbidity[160].

In girls an untreated recurrence may endanger mother and child, if incarceration happens during pregnancy. A recently published systematic review of pregnant women with diagnosis of Bochdalek's hernia revealed a substantial risk of maternal and/or fetal death and preterm delivery. The incidence of bowel obstruction, ischemia or perforation was 44% and the risk of adverse outcome consequently increased. The authors therefore concluded that diagnosis and surgical repair should be achieved as early as possible[161]. In herniated kidneys hydronephrosis with loss of renal function and secondary arterial hypertension due to pelviureteric obstruction or compression of the renal vessels can result[162].

Hiatal hernia is caused by distraction of the diaphragmatic crura from the oesophagus especially in patients with a hypoplastic medial diaphragm and initial intrathoracic stomach-herniation. It may or may not be associated with relevant GER and failure to thrive. Long-term-GER may cause pulmonary compromise due to repetitive microaspirations and Barrett's esophagus at older age.

4.1.1 Time

Early recurrence

Reviewing literature there are several studies on recurrence rates after surgical repair of CDH, but one has to differentiate between early recurrences within the first hospital stay and late recurrences thereafter. 2011 Gander[163] reported on 23% early recurrences after thoracoscopic repair versus 0% early recurrence after open surgery in 26 MIS- and 19 OS-patients. Nagata[164] observed an early recurrence rate of 2.8% and a late recurrence rate of 8.9% in a multicentre retrospective survey including 180 patients. According to the CDH-registry, which for this analysis included a total of 4390 operated CDH-patients (of whom 151 underwent thoracoscopic repair), CDH recurred early in 2.7% of conventionally operated patients and in

[158] Antiel et al. (2017)
[159] Burgos et al. (2017b)
[160] Testini et al. (2017); Portelli et al. (2021); Ramspott et al. (2021)
[161] Choi et al. (2021)
[162] Ramspott et al. (2021)
[163] Gander et al. (2011)
[164] Nagata et al. (2015)

7.9% after thoracoscopic repair[165]. In another study from the CDH-study group Putnam[166] reported an overall early recurrence rate of 2.3% in 3332 patients who underwent CDH-repair between 2007 and 2015. Annual recurrence rates after laparotomy ranged from 1.1% to 3.7% and after thoracoscopy from 1.7% to 8.9%.

In our cohort of 410 patients – operated at a single institution over a time-period of 10 years – early recurrence until discharge was very low compared to literature reports (0.7%) and therefore no difference concerning the technique of CDH-repair (open versus MIS) could be identified.

Late diaphragmatic complications

Concerning the time of recurrence after discharge, this complication has been observed rather early in several reports. Of 24 recurrences in 238 patients reported by Fisher, 58% of patients developed recurrence within six months and 79% within one year of life[167]. Tsai observed all of their seven recurrences within the first year of life, but especially patients without significant pulmonary morbidity were not followed long-term[168]. Al-Iede reported on recurrence being detected at an average age of 19.8 weeks (ranging from 15 to 34 weeks, also including six patients with MIS-repair)[169]. Jancelewicz published a median time of recurrence of 0.7 years (ranging from 0 to 8.5 years)[170]. 70% of recurrences were detected before the age of two years and 17% after four years of age. 65% of patients were reported to have been asymptomatic.

In our patient-cohort only 51% of diaphragmatic complications after discharge were diagnosed within the first year of life and 83% within the first two years of life. Thus 17% recurred beyond two years of age, and 9% beyond four years of age. Only one patient presented with acute incarceration (2.6%), while the majority (97.4%) showed either no or minor and unspecific symptoms and was diagnosed by radiologic imaging in our follow-up-program or incidentally during abdominal surgery for other reasons (small bowel obstruction due to adhesions, fundoplication due to gastro-oesophageal reflux). This emphasizes the importance of a structured follow-up program until adolescence and regular radiologic imaging also in apparently asymptomatic survivors of CDH.
With implantation of a broad cone-shaped, non-absorbable patch and meticulous surgical technique recurrence may develop by growth, but a lower incidence and a shift to older age can be observed – reducing the need for secondary surgery in early infancy with its higher

[165] Tsao et al. (2011)
[166] Putnam et al. (2017)
[167] Fisher et al. (2009)
[168] Tsai et al. (2012)
[169] Al-Iede et al. (2016)
[170] Jancelewicz et al. (2013)

complication-rate and possibly negative side-effect of general anaesthesia on cerebral and neurologic development: A relevant hypercapnia and acidosis have been observed in neonates undergoing CDH-repair, regardless whether it was an open or minimally-invasive operative approach[171]. Animal studies have shown hypercapnia and acidosis after initiation of general anaesthesia and histologically detected a relevant brain cell death and neurocognitive deficits, which has risen concerns for anaesthesiology during infancy[172].

Reports on CDH-recurrence and its impact on chronic gastrointestinal morbidity and potential late mortality are limited but there seems to be a correlation beyond the first year of life that is devastating for patients and families[173]. Also, in a multivariate analysis it could be shown, that mortality as well as the number of reoperations are significantly increased in patients with complications within one year after CDH-repair[174].

In our cohort, nonspecific symptoms associated with diaphragmatic complications were mainly gastrointestinal (43.2%) and less often respiratory (13.5%). Of course, these could also be dependent on internal comorbidities of congenital diaphragmatic hernia and therefore be overlooked or undervalued. Accordingly, failure to thrive could also be associated with and explained by persistent pulmonary hypertension, increased respiratory effort due to lung hypoplasia, associated malformations and adhesions. When comparing weight of R- and nonR-patients it seems evident, that two thirds of R-patients showed less thriving than nonR-patients. However, chronic gastrointestinal problems and late mortality due to an underlying recurrence of CDH could be prevented, if diagnosed and treated timely.
Furthermore, two recently published reviews provide an insight into complications and mortality in adults with late-presenting CDH, which was thought to be a harmless situation. With less than 100 cases, left-sided CDH is rarely diagnosed in adults but seems to be correlated with a high rate of gastrointestinal complications and mortality[175]. Right-sided CDH is also a rare condition in adults with 44 patients being reported so far. Mainly, herniation of small and large intestine has been observed - necessitating bowel resection due to intestinal ischemia or perforation in 23% and showing a mortality-rate of 9%[176]. In 16 of 39 patients (41%) with congenital Bochdalek hernia or CDH becoming evident during pregnancy severe complications (intestinal obstruction, gastric gangrene, volvulus, ischemic bowel necrosis, splenic infarction and/or cardiorespiratory failure) have led to emergency surgery[177]. Alike in our patient-cohort,

[171] Zani et al. (2017)
[172] Stratmann et al. (2009)
[173] Burgos et al. (2017b)
[174] Heiwegen et al. (2020)
[175] Portelli et al. (2021)
[176] Ramspott et al. (2021)
[177] Testini et al. (2017)

patients in adulthood also presented with mainly gastrointestinal symptoms. There have been few reports on symptomatic hydronephrosis and/or arterial hypertension in patients with herniated kidneys, that resolved after surgical repair of the diaphragmatic defect[178]. Therefore, CDH containing abdominal viscera is considered to be an emergency in adults that should be repaired as soon as possible to reduce mortality and morbidity[179]. On the other hand, the presence of a small Bochdelak hernia containing omentum or fatty tissue has been reported more frequently in CT-scans performed for other reasons[180]. This condition is usually described as an incidental finding in asymptomatic patients and may be managed expectantly.

The apparently substantial risk of gastrointestinal morbidity and late mortality in patients with visceral (re-)herniation emphasizes the importance of a standardized follow-up program until adolescence and regular radiologic imaging also in apparently asymptomatic CDH-survivors to evaluate the real long-term prevalence of recurrence and morbidity that will otherwise be unrecognized and underestimated. Furthermore, a hidden mortality may be attributed to unrecognized CDH-recurrence that cannot be detected in retrospective studies and those lacking long-term follow-up. CDH is a rare malformation and paediatricians and general practitioners looking after these patients after discharge from the hospital may not be aware of CDH-recurrence as a complication, that may present with nonspecific gastrointestinal symptoms and become life-threatening within a short time after the first onset of symptoms. Alike in adulthood, the risk of morbidity and mortality is likely to be higher in patients undergoing emergency surgery – while on the other hand, these could be lowered in patients operated in an elective setting. In future, larger prospective cohort-studies should be able to provide an answer to this hypothesis.

4.1.2 Laterality of CDH

Hajer described a difference in recurrence between right-sided CDH (44%) and left-sided CDH (9%)[181]. The predominance of CDH-recurrence in right-sided CDH was confirmed by Beaumier[182]. They had an incidence of 17% right-sided CDH among 498 multicentre-patients with a higher patch-rate compared to left-sided CDH (48.2% versus 30.6%) and a higher recurrence rate (4.1% versus 0.6%). Collin also reported on a significantly increased recurrence rate in right-sided CDH (5/10 patients with r-CDH versus 6/39 patients with l-CDH, p=0.03). In this cohort of 49 patients there was also a higher rate of patch implantation in right-

[178] Ramspott et al. (2021)
[179] Testini et al. (2017); Portelli et al. (2021); Ramspott et al. (2021)
[180] Mullins et al. (2001); Garófano-Jerez et al. (2011)
[181] Hajer et al. (1998)
[182] Beaumier et al. (2015)

sided CDH (50% versus 20.5%)[183]. Duess observed no significant difference in recurrence rate between right- and left-sided CDH in 178 patients of three centres (9.4% versus 8.9%) with a comparable incidence (18% right-sided CDH) and an equally distributed patch-rate (40.6% in right-sided CDH and 40.4% in left-sided CDH)[184]. Fisher also did not observe a difference in recurrence rate between right- and left-sided CDH in 238 patients treated at a single institution (21% versus 13%, p=0.34)[185].

In contrast, we observed a lower recurrence rate in right-sided CDH with only one recurrence in 62 survivors (1.6%) compared to 37 diaphragmatic complications in 262 survivors with left-sided CDH (14.1%). This difference was statistically significant (p<0.004). We had a similar incidence of right-sided CDH compared to literature reports (19%), but in contrast a much higher patch-rate within our cohort – although this did not differ between right- and left-sided CDH (82.3% in r-CDH versus 78.6% l-CDH, p=0.6). In our patient-cohort the relative risk for diaphragmatic complications was increased significantly 8.5-fold for patients with left-sided CDH.

The higher incidence in left-sided CDH is a consequence of intestine re-protruding into the thoracic. In right-sided CDH the liver is too large and may be adherent to the patch and thus well covering the recurrent defect from below. Small recurrences may also develop with growth in right-sided CDH but may not cause any problems and may not be detected by radiological imaging due to absent re-herniation of abdominal viscera.

4.1.3 ECMO-therapy

Furthermore, differences in recurrence rate have been reported for ECMO- and nonECMO-patients (36% versus 9%) by Hajer in 1998[186] and Moss in 2001 (57% recurrence rate in ECMO-patients, 27% in nonECMO-patients)[187]. Janssen calculated an increased odds ratio for recurrence in patients receiving ECMO-therapy (OR=6.3) and patients requiring ECMO-therapy and patch-repair (OR=11.2)[188]. On the other hand, Fisher did not observe a significant difference between ECMO- and nonECMO-patients (6 recurrences in 46 ECMO-patients (13%) versus 18 recurrences in 192 nonECMO-patients (9.4%), p=0.42)[189]. Data from the CDH-study group comprising 3332 operated CDH-patients did not reveal an influence of ECMO-therapy on early recurrence rate[190].

[183] Collin et al. (2016)
[184] Duess et al. (2015)
[185] Fisher et al. (2009)
[186] Hajer et al. (1998)
[187] Moss et al. (2001)
[188] Janssen et al. (2017)
[189] Fisher et al. (2009)
[190] Putnam et al. (2017)

In our cohort there was also no significant difference between ECMO- and nonECMO-patients in the long-term (ECMO 14.5% versus nonECMO9.7%; p=0.22) – even though there was a highly significant difference in the necessity for patch-closure of the diaphragmatic defect between both patient groups (96.2% patch-rate in ECMO-patients versus 67.9% patch-rate in nonECMO -patients; p<0.000001). Also, the need for an abdominal wall patch was significantly higher in ECMO-patients (32.8% versus 6.1% in nonECMO-OS-patients; p<0.000001). These differences reflect CDH-severity in our ECMO-cohort, which was nonetheless not correlated with a significant difference in complication-rate with our technique of diaphragmatic reconstruction using a cone-shaped patch.

4.1.4 Defect size

The CDH-study group reported an incidence of defect size A and B of 50% in open surgery and identified larger defect size to be an independent risk-factor for in-hospital-recurrence in 3332 operated CDH-neonates[191]. To date, there are no further studies reporting on defect size and recurrence rate. Almost all reports lack information about size-classification, which makes it difficult to reliably compare recurrence rates in general.

In our open-surgery cohort the incidence of defect size A and B was only 28.6%. Nevertheless, we observed a very low in-hospital recurrence rate (0.7%), so that no influence of defect size on recurrence rate could be identified. In-hospital-recurrences might therefore rather be due to technical issues concerning diaphragmatic reconstruction in larger defects. Several surgical steps might be crucial to prevent early recurrence: using non-absorbable material for patch and sutures, reducing tension on the hypoplastic diaphragmatic rim by implanting a cone-shaped patch, using a ‘dualmesh’ to ease incorporation with muscle fibres and surrounding tissue, using pledget-sutures on the diaphragm to prevent the sutures from cutting through the muscle and additional fixation of an overlapping patch-border to promote adhesions between the patch and surrounding tissue.
First, we were able to show that the risk of late diaphragmatic complications correlates with the initial defect size and is significantly higher in larger defects in open abdominal surgery (figure 16). Late complications are rather caused by patient-growth: either a recurrent defect at the original localization develops because the patch might get distracted from the ribs and not enough fibrous tissue might have developed to cover the distance or the diaphragmatic crura are distracted and secondary hiatal hernia develops. Naturally, this is more likely to happen in patients with only a hypoplastic diaphragmatic remnant: patients with defect size D were most likely to develop complications in the long-term (37.5%), while patients with defect

[191] Putnam et al. (2017)

size A did not in our open-surgery cohort. In patients with defect size B rcompliation-rate was also very low (2.8%), while it was observed in 13.1% of patients with defect size C. Given the fact that the majority of patients with open surgery treated at our institution had large diaphragmatic defects (71.4% defect size C and D) and all of these required patch-repair, the long-term complication-rate of 17% was comparatively low in these high-risk-patients.

4.1.5 Type of CDH-repair

A difference in recurrence rate in open surgery after primary reconstruction of the diaphragm and patch implantation has been reported by Jancelewicz in 2010. CDH was observed to recur in 46% after patch implantation and in 10% after primary repair in a cohort of 99 CDH-survivors, who were seen in a multidisciplinary follow-up-clinic with regular radiologic imaging at an age of 0.2 to 10.6 years. A patch implantation was necessary in 58%[192]. In a retrospective study over 12 years published in 2013 by the same author a recurrence rate of 15% was observed in 187 patients, of whom 27% underwent patch-repair[193]. In 2001 Moss already reported on a recurrence rate of 41% in 29 surviving CDH-patients after patch implantation within three years and concluded that it “is not a long-term solution” for these children[194]. Nasr treated 188 patients at a single institution over 37 years. They did not observe recurrence after primary repair (137 patients) but in 10.5% after diaphragmatic reconstruction with a muscle flap in 19 patients and in 25% after patch-repair in 32 patients[195]. In a large single-centre study of 238 consecutive patients Fisher reported eight recurrences in 128 patients after primary repair (6.25%) and 16 in 110 patients after patch-repair (14.5%; p=0.05) within a maximum follow-up time of 51 months. After open abdominal surgery CDH recurred in 22 of 231 patients (9.5%). Diaphragmatic reconstruction was performed by a prosthetic patch in 46% of patients, but in the recurrence-cohort patch-rate was 67%[196]. Only Riehle reported a low recurrence rate of only 4% in 28 surviving patients after patch-repair treated at a single institution over 20 years with a follow-up-time of a minimum of two months to a maximum of 115 months. It was a retrospective study and the authors state themselves, that the recurrence rate may be underreported due to lacking a structured follow-up[197]. In a recently published review on morbidity after CDH-repair, the risk of recurrence was reported to be 3.6 times higher after open patch-repair[198].

[192] Jancelewicz et al. (2010)
[193] Jancelewicz et al. (2013)
[194] Moss et al. (2001)
[195] Nasr et al. (2010)
[196] Fisher et al. (2009)
[197] Riehle et al. (2007)
[198] Heiwegen et al. (2021)

In our cohort there was no significant difference regarding long-term complication-rate in open surgery after primary repair (8.8%, 68 patients) and after implantation of a cone-shaped patch (12.7%, 251 patients) with follow-up of a minimum of two years to a maximum of ten years (p=0.5275). The only previous study reporting on a similar recurrence rate for primary and patch-repair in open surgery was published by Tsai in 75 surviving primary repair-patients (4% recurrence) and 74 surviving patch-patients (Goretex®, 5.4% recurrence) treated in a single-institution between 1999 and 2010. An implantation of a dome-shaped patch was performed in 53.8% (99 of 184 initially operated neonates). All recurrences were diagnosed within the first year of life, while especially patients without significant lung disease have not been observed long-term. They suggested that high recurrence rates after patch-repair are rather due to technical aspects[199]. In our OS-cohort complication-rate within the first year of life was 5.9% for primary and 6.2% for patch-repair. The overall recurrence rate is therefore similar in both study-cohorts (p=0.67) even though an overall patch-rate of 72.4% was significantly higher in our patient-collective (99 of 184 initially operated patients (53.8%; Tsai) versus 297 of 410 initially operated patients (72.4%; our collective), p=0.000013). In our cohort there was no significant difference between patients with and without diaphragmatic complications (p=0.53). Also, Heiwegen reported no difference in recurrence rate between primary repair and patch repair patients (6% both) within one year of follow-up in a retrospective study of 197 patients. In 39.6% of all patients a dome-shaped patch was implanted[200]. In comparison to the only prospective cohort study of 56 patch-patients and a recurrence rate of 46% our long-term complication rate of 12.7% after implantation of a nonabsorbable, broad cone-shaped patch was significantly lower (p<0.001)[201].

Earlier results from our centre showed recurrence rates of 46% in 13 patients with a plane patch, 11% after implantation of an ‘oversized patch’ in 9 patients and 9% in 11 patients with a cone-shaped patch after one year of follow-up[202]. Also in the long-term, a rate of diaphragmatic complications of only 12.7% after implantation of a cone-shaped Goretex®-patch remained lower than most of the results published in literature - especially when taking into account that this is the largest single-centre cohort of patch-patients that has been followed in a structured follow-up program with regular radiologic imaging.

Recurrence after diaphragmatic reconstruction with a patch may rather depend on the technique of implantation than on the necessity for patch implantation itself. The utilization of oversized-patches in a cone-shape seems to significantly reduce complication-rate compared to plane patches that are directly sutured to the diaphragm – as is indicated by this longitudinal

[199] Tsai et al. (2012)
[200] Heiwegen et al. (2020)
[201] Jancelewicz et al. (2010)
[202] Loff et al. (2005)

follow-up-study. Furthermore, the creation of an overlapping edge to promote adhesions to the surrounding tissue is in our opinion crucial to prevent long-term recurrence. In our experience, the broad cone-shaped patch allows for a flattening with growth and thus an enlarged diameter, which reduces tension on the hypoplastic diaphragm also in the long-term. Most recurrences after primary repair in our cohort were detected until 2007 and only one since 2008 in a patient with defect size B. It seems to be essential to reduce tension on the diaphragm to reduce recurrence rate and therefore patch implantation is now rather frequent in defect size B (80.5%).

The establishment of a standardized long-term-follow-up-program for all patients after neonatal CDH-repair should be mandatory to reliably detect recurrence - because most recurrences may not be accompanied by any or just unspecific minor symptoms (e.g. feeding problems, constipation, GER, tachypnea) and, in our experience, develop in children older than 12 months of age in about 45% of all cases. Recurrence rates are certainly underestimated in studies that did not perform long-term surveillance in all surviving CDH-patients.

4.1.6 Patch material

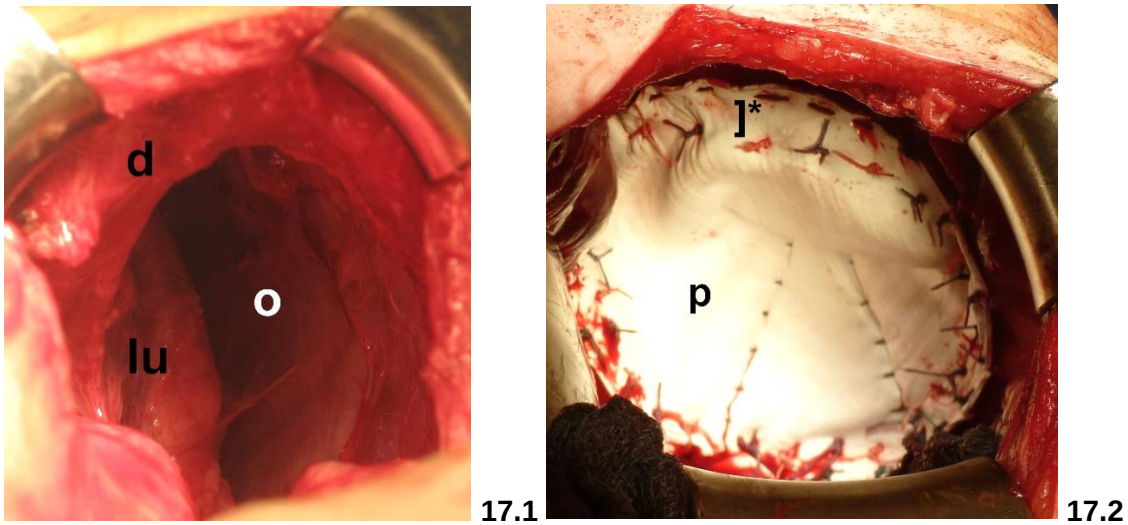


Figure 17: intraoperative situation in CDH-recurrence in a 2-year old boy after implantation of an absorbable patch in defect size C; 17.1 recurrence due to absorbed Tutopatch® (o=translucent membrane, d=diaphragm, lu=lung; 17.2 closure of recurrence with large cone-shaped Goretex-Dualmesh®-patch (p) and additional fixation to diaphragm and abdominal wall with overlapping border ( ])*

Differences in recurrence rates depending on patch material have also been described. As reported by Jancelewicz the highest risk for recurrence was associated with the use of absorbable patches with an overall recurrence rate of 46% after patch implantation (Surgisis®: 68% in 23 patients; Goretex®: 44% in 16 patients; mesh-patch (Goretex®+Surgisis®): 27% in 15 patients). Furthermore, they observed multiple recurrences in 37% of patients, of whom 91% received Surgisis® as patch material[203]. Jawaid reported their only two recurrences in 102 CDH-survivors after implantation of absorbable patches (Surgisis®) in two patients, while 35 patients remained without recurrence after Goretex®-use in 20 years[204]. Ramadwar already concluded in 1997 that collagen-coated Vicryl-mesh is not a suitable material for reconstruction of diaphragmatic hernias[205].

In contrast, no difference in short-term recurrence rate between absorbable Surgisis®-patch (44% in 27 patients) and non-absorbable Goretex®-patch (38%, 45 patients) was observed by Grethel in 2006[206]. These findings were confirmed by Romao concerning their own 22 patch-patients over 10 years (31% Surgisis® versus 33% PTFE) and concerning a meta-analysis with one further study adding up to 40 Surgisis®-patients and 54 PTFE-patients[207].

A 25% recurrence rate each was reported by Peter in a retrospective study of 81 CDH-survivors (Surgisis®: 13 patients, mesh-patch: 11 patients)[208]. A similar recurrence rate of 25% was reported for 32 Goretex®-patients by Nasr in a retrospective review of 188 children (1969-2006), a patch-repair in 27% and a median follow-up time of 7 years[209].

In another study Goretex® had a recurrence rate of 28% in 29 patients compared to 0% after the use of biodegradable Permacol™ in eight patients within a median follow-up-time of 20 months[210]. Laituri also reported on a higher recurrence rate after implantation of non-absorbable patch material (22% in 37 Surgisis®-patients versus 40% in 5 Alloderm®-patients versus 50% in 12 non-absorbable patch-patients). They also noticed a higher re-recurrence rate and therefore abandoned the use of non-absorbable patches (50% Surgisis® versus 100% Alloderm® versus 67% non-absorbable patch material)[211]. More recently, the use of biological patches has even been disapproved due to significantly higher recurrence rates[212].

Low recurrence rates after the use of non-absorbable patches were reported by Riehle: 4% after the use of a Goretex®-patch in 28 surviving patients within a follow-up-period of two to

[203] Jancelewicz et al. (2010)
[204] Jawaid et al. (2013)
[205] Ramadwar et al. (1997)
[206] Grethel et al. (2006)
[207] Romao et al. (2012)
[208] St Peter et al. (2007)
[209] Nasr et al. (2010)
[210] Mitchell et al. (2008)
[211] Laituri et al. (2010)
[212] de Haro Jorge et al. (2021)

115 months [213] and Tsai: 5.4% after implantation of a dome-shaped Goretex®-patch in 74 surviving patients[214].

In our cohort solely non-absorbable material was used for patch implantation (Goretex Dualmesh®) and sutures (Ethibond® and Ticron®). Our overall complication rate of 12.4% in 258 patch-patients in open surgery over a follow-up period of a minimum of two years to a maximum of ten years reflects, that long-term results strongly depend on technique of implantation with non-absorbable patch material. Only five re-recurrences were observed in 258 patch-patients (1.9%), which is also very low compared to literature (up to 67%)[215]. In our experience recurrence size is much larger after utilization of absorbable patch material. The advantage of using non-absorbable patch material is, that the original defect size proportionally minimizes in size with growth, while it will stay relatively the same after implantation of absorbable patch material. Additionally, the size of the recurrent defect is smaller after implantation of nonabsorbable patches that are usually well incorporated. Therefore, surgical repair of recurrence can be obtained by a smaller secondary patch with non-absorbable material rather than complete substitution of the formerly implanted absorbable patch (figure 16-18).

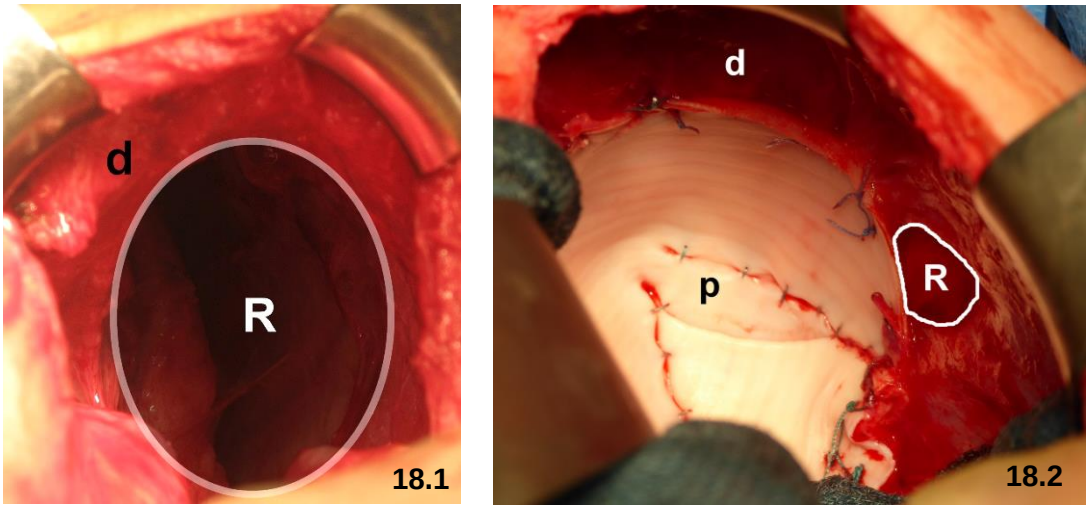


Figure 18: difference in size of CDH-recurrence in initial defect size C (d=diaphragm, R=recurrence, p=patch); 18.1 after implantation of an absorbable Tutopatch®: recurrence size = original defect size; 18.2 after implantation of a non-absorbable Goretex-Dualmesh®-patch: recurrence size << original defect size

[213] Riehle et al. (2007)
[214] Tsai et al. (2012)
[215] Gasior and St Peter (2012)

4.1.7 Type of abdominal closure

Fisher first identified the implantation of an abdominal wall patch as an independent risk-factor for CDH-recurrence[216]. Furthermore, there has been a recent publication calculating a significantly increased odds ratio of CDH-recurrence within one year for patients requiring an abdominal wall patch (11.3, 95% CI 1.5-84.4)[217].

In our patients, this was also reproducible – but we are the first to show that the abdominal wall patch clearly reflects disease severity: a significantly higher incidence of intrathoracic liver and stomach in left-sided CDH, need for ECMO-therapy and patch-repair and larger defects were observed in these patients as compared to patients without abdominal wall patch. In our cohort, also a significantly increased, yet lower risk for diaphragmatic complications was identified in patients with an abdominal wall patch (3.2; 95% CI 1.8-5.8, p<0.001).

4.2 Proposal of a risk-stratified approach to diaphragmatic complications

Based on our findings and current literature review and considering the seemingly substantial risk of complications later in life, I would like to propose a risk-stratified approach to the treatment of diaphragmatic complications: boys with herniation of omentum or upper pole of the kidney may be managed expectantly with detailed counselling of parents and ongoing follow-up, while in girls the risk of enlargement of the diaphragmatic defect and secondary herniation of abdominal viscera during future pregnancy should also be considered. Patients with herniation of intestine, symptomatic hydronephrosis of the herniated kidney, arterial hypertension or relevant gastroesophageal reflux as confirmed by endoscopy and 24-hour ph-(impedance-) testing should rather undergo secondary surgery to prevent morbidity associated with chronic diaphragmatic complications as explained above. Regarding timing of recurrence repair it should also be taken into consideration that the recurrent defect will become larger with ongoing growth, which can make repair more difficult. In chronic recurrence repetitive inflammatory stimuli may cause more severe adhesions of the herniated viscera[218] and increase the risk of intraoperative laceration. Furthermore, a seemingly uncomplicated diaphragmatic hernia or recurrence can become a life-threatening condition at any time. Prior to surgery pulmonary hypertension, obstructive pulmonary compromise and a catabolic metabolic status should be excluded or treated accordingly to reduce perioperative complications.

[216] Fisher et al. (2009)
[217] Heiwegen et al. (2020)
[218] Testini et al. (2021)

5 CONCLUSION

In conclusion**,** our cohort of 508 patients within 10 years is the largest prospective long-term study that has been reported from a single institution with a standardized surgical treatment algorithm, a structured long-term-follow-up for all surviving CDH-patients and a participation-rate of more than 90%. This allows for a reliable assessment of recurrence rate and determination of significant risk factors. For surgical correction of large CDH a cone-shaped patch was implanted as a standardized procedure. Only non-absorbable patch material (Goretex Dualmesh®) and non-absorbable sutures (Ethibond® and Ticron®) were used for an overlapping fixation. Long-term rate of diaphragmatic complications in 258 surviving and longitudinally reassessed patch-patients after open abdominal surgery was 12.4% within an observational time of a minimum of two years and a maximum of ten years. Recurrence rate until discharge was very low (0.7%). Comparing our results to studies in literature is difficult, because most of these are retrospective and did not offer a structured follow-up with regular radiologic imaging to all surviving CDH-patients. Therefore, most reported recurrence rates are most certainly underestimated. Yet, much higher recurrence rates of 44% have been reported after implantation of a Goretex®-patch in the only comparable long-term study by Jancelewicz in 2010[219].

A reduced rate of diaphragmatic complications in open surgery can even be achieved in a CDH-referral centre with a high incidence of patch implantation (79.1% overall, 96.2% in ECMO-patients) and a predominance of defect size C and D (71.4% overall, 85.1% in ECMO-patients) with a standardized technique even though numerous surgeons may be involved.

The larger the initial defect, the more likely is recurrent diaphragmatic hernia with ongoing growth. As independent variables for diaphragmatic complications the need for an abdominal wall patch (as reflecting disease-severity) and left-sided CDH could be identified in multivariate analysis, as well as a liver-herniation in left-sided CDH. High-risk patients are nowadays already identified on prenatal investigation: intrathoracic liver-position in left-sided CDH, small fetal lung volume and consequently estimated large defect sizes. It has been shown that these patients are more likely to require postnatal ECMO-therapy and diaphragmatic reconstruction with a patch and that they are at risk of early mortality and long-term morbidity. These patients should therefore be transferred to a high-volume centre for optimized treatment.

[219] Jancelewicz et al. (2010)

With improvement of survival also of neonates with large diaphragmatic defects a higher rate of long-term morbidity can be observed also in regards to surgical complications. In-hospital recurrence most probably results, if the diaphragmatic defect has been closed with too much tension, while late diaphragmatic complications (recurrence and secondary hiatal hernia) develop with growth especially in patients with only a hypoplastic diaphragmatic remnant in large defect sizes. With meticulous technique and implantation of a nonabsorbable cone-shaped patch it is possible to achieve low early and late recurrence rates. Late complications are clearly associated with initial defect size. A reduction of tension can be achieved by a more liberal implantation of prosthetic patches. It is important to dissect the diaphragmatic medial and posterior rim in large defects to promote its growth by suturing the patch onto it.
The cone-shaped patch reduces the intrathoracic volume, which is not needed by the hypoplastic lung in the beginning. There is still enough room left for the lung to expand in the long-term. On the other hand, intra-abdominal space is enlarged – which helps the surgeon to replace the abdominal organs in an anatomical position and to close the abdominal cavity without or with less tension and thus reducing the need for an abdominal wall patch. Tension to the diaphragm is also reduced by the three-dimensional shape, both initially and by flattening of the cone during growth. Furthermore, a physiologic contour of the diaphragm results. By a special suturing technique with additional fixation of an overlapping border to the diaphragm and abdominal wall the contact between prosthetic material and surrounding tissue is enlarged to promote tight adhesions and the development of fibrous tissue - thus the incidence of ‘true’ recurrence may be reduced also in patients with large diaphragmatic defects.

We also recommend the utilization of non-absorbable patches and sutures, because with growth the diaphragmatic defect will proportionally minimize in size and the size of the recurrent defect is smaller than after utilization of an absorbable patch.

With a thorough implantation technique of the diaphragmatic patch growth may cause distraction of the diaphragmatic crura from the oesophagus especially in patients with only a hypoplastic medial diaphragmatic rim and initial intrathoracic herniation of the stomach. This can result in secondary hiatal hernia, which may require hiatoplasty and fundoplication if associated with a relevant gastroesophageal reflux.

Unlike previous reports, diaphragmatic complications occurred within the first year of life in only half of our patients. Furthermore, our findings seem to reveal that recurrence-patients mostly present nonspecific gastrointestinal symptoms and failure to thrive, which can easily be misinterpreted and increase the risk of morbidity and mortality in undiagnosed CDH-recurrence. This seems to underline the importance of radiologic screening during follow-up.

A native chest X-ray seems to be appropriate to detect or at least suspect CDH-recurrence in most patients (94.6%). Additional imaging (CT, MRI, contrast study) may be helpful in cases of doubt. Recurrence rates therefore certainly have been underestimated in other previously published studies that did not offer long-term follow-up to all CDH-patients. Yet, it is very important to diagnose and treat recurrence with re-herniation of intestine or kidney and secondary hiatal hernia with relevant gastroesophageal reflux on time to be able to prevent recurrence related chronic gastrointestinal morbidity and acute incarceration with their impact on long-term prognosis.

6 SUMMARY

Congenital diaphragmatic hernia is a rare defect with an incidence of 1:3000 in neonates and patients present complex hemodynamic, respiratory and reconstructive challenges. Nowadays it is still a life-threatening condition and survivors may suffer from long-term-morbidity that also influences quality of life. In large defects a substitute for the diaphragm is required, while different techniques have been described and different patch materials have been used. Recurrence is one of the most severe surgical complications after repair of congenital diaphragmatic hernia with an increased risk of intestinal injury at secondary surgery. In literature incidence varies depending on operative technique, patch material and patient selection between 4% and more than 50%. But studies are difficult to compare, because operative techniques and patch material differ, most are retrospective and do not offer a structured long-term-follow-up to all surviving patients with congenital diaphragmatic hernia. Previously reported recurrence rates therefore certainly have been underestimated. Over the years still high recurrence rates are reported in recent literature after patch repair. This is the largest prospective long-term-study that has been reported from a single institution with a standardized surgical treatment algorithm and a structured long-term-follow-up offered to all surviving patients with a participation-rate of more than 90%.

The purpose of this prospective study was to evaluate the impact of surgical techniques on the rate of recurrence in open surgery. Data was collected over a time period of 12 years with a minimal follow-up time of two years to detect incidence and time of recurrence depending on different operative procedures. Between 2003 and 2007 open surgery was performed, since 2008 minimally invasive techniques were also applied. 508 neonates with congenital diaphragmatic hernia were treated at our institution between 2003 and 2012, of whom 200 received extracorporeal membrane oxygenation therapy (ECMO-therapy). 442 patients (87%) underwent surgical closure of the diaphragm, in 47 minimally invasive surgery was applied (10.6%). In open surgery a cone-shaped patch was used in 301 neonates to achieve closure of the diaphragm (76.2%). Overall 410 patients survived (80.7%) and the majority was reassessed in our longitudinal follow-up program also comprising regular radiologic imaging (90.2%).

Early recurrence until discharge was observed in only three of 410 surviving patients (0.7%). In 28 of 326 surviving and reassessed children late recurrence occurred after open surgery (8.6%). In six patients multiple recurrences were detected (1.8%). Recurrence at the original localization of the diaphragmatic defect (‘true’ recurrence) was detected in 24 cases (7.4%), an isolated hiatal hernia in eight (2.5%) and a combination of both in six (1.8%).

Overall 38 recurrences were diagnosed (11.7%), 19 in 131 surviving ECMO-patients (14.5%). Recurrence rate after primary repair was 8.8% (6/68 patients) and 12.7% after repair with a cone-shaped patch (32/251 patients). According to defect size higher recurrence rates were detected in larger defects (defect A 0%, defect B 2.8%, defect C 13.1%, defect D 37.5%).
Recurrence after repair of congenital diaphragmatic hernia was observed within 12 months after surgery in 21 cases (55.3%), and within 24 months in 32 cases (84.2%).

Long-term-results after diaphragmatic reconstruction highly depend on surgical technique. With the use of a cone-shaped Gore-Tex®-patch long-term overall recurrence rate was 12.7% in open surgery within an observation period of a minimum of two years to a maximum of ten years. As independent variables for recurrence of diaphragmatic hernia a left-sided defect and the need for an abdominal wall patch could be identified as well as a ‘liver-up’-situation in left-sided diaphragmatic hernia.
It is essential to follow these patients in a distinct long-term follow-up program with regular radiologic imaging – since most recurrences were detected in patients who showed no or minimal clinical symptoms (97.4%) and because 44.7% of recurrences were diagnosed beyond one year of age. Only a structured follow-up with regular radiologic imaging of all surviving patients with congenital diaphragmatic hernia allows a reliable detection of recurrence. If waiting for symptomatic patients, the vast majority will not be diagnosed bearing the risk of intestinal incarceration, bowel gangrene and lethal septicaemia.

7 ZUSAMMENFASSUNG

Die angeborene Zwerchfellhernie gehört mit einer Inzidenz von 1:3000 zu den seltenen Fehlbildungen und betroffene Neugeborene stellen Neonatologen und Kinderchirurgen vor komplexe hämodynamische, respiratorische und rekonstruktive Herausforderungen. Auch beeinflusst die Langzeit-Morbidität die Lebensqualität. Bei großen Defekten wird ein Ersatz für das Zwerchfell benötigt, der mit verschiedenen Techniken und unterschiedlichen Patchmaterialien erreicht werden kann. Das Rezidiv gehört zu den schwerwiegendsten chirurgischen Komplikationen nach Korrektur der angeborenen Zwerchfellhernie. In der Literatur schwanken die Angaben hierzu je nach Operationstechnik, Patch-Material und Patientenselektion zwischen 4% und mehr als 50%. Allerdings sind die verschiedenen Studien schwierig zu vergleichen, da Operationstechniken und Patchmaterialien differieren, die meisten retrospektiv sind und keine strukturierte Nachsorge für alle überlebenden Kinder mit Zwerchfellhernie anbieten. Daher sind publizierte Rezidivraten sicherlich unterschätzt worden. Immer noch werden hohe Rezidivraten nach Patch-Verschluss in der aktuellen Literatur angegeben. Dies ist die größte prospektive Untersuchung an einem Zentrum mit standardisiertem operativen Behandlungsalgorithmus und einem strukturierten Nachsorge-programm für alle überlebenden Kinder mit Zwerchfellhernie, an dem mehr als 90% teilnehmen.

Ziel dieser Doktorarbeit war es, den Einfluss verschiedener offener Operationstechniken auf die Rezidivrate prospektiv zu untersuchen. Die Patientendaten wurden über einen Zeitraum von 12 Jahren erhoben, um eine minimale Nachbeobachtungszeit von 2 Jahren zur Beurteilung der Inzidenz und des Zeitpunkts des Auftretens von Rezidiven abhängig von verschiedenen Operationstechniken beurteilen zu können. Zwischen 2003 und 2007 wurde offen operiert, seit 2008 wurden auch minimal-invasive Techniken angewendet. 508 Neugeborene mit angeborener Zwerchfellhernie wurden zwischen 2003 und 2012 an unserer Klinik behandelt, von denen 200 eine extrakorporale Membranoxygenierung (ECMO-Therapie) erhielten. 442 Patienten (87%) wurden operiert und bei 47 erfolgte dies minimal-invasiv (10.6%). Beim offenen Operationsverfahren wurde bei 301 Neugeborenen ein Kegelpatch zur Zwerchfellrekonstruktion verwendet (76.2%). Insgesamt überlebten 410 Patienten (80.7%) und die Mehrheit wurde im Rahmen unseres longitudinalen Nachsorgeprogrammes, das auch eine regelmäßige radiologische Bildgebung umfasst, nachuntersucht (90.2%).

Ein frühes Rezidiv bis zur Entlassung aus der initialen stationären Behandlung trat nur bei drei von 410 überlebenden Patienten auf (0.7%). Bei 28 von 326 überlebenden und nachuntersuchten Kindern nach offenem Operationsverfahren wurde ein Spät-Rezidiv diagnostiziert (8.6%). Bei sechs Patienten traten multiple Rezidive auf (1.8%). Ein Rezidiv im Bereich des initialen Zwerchfelldefektes (‚echtes' Zwerchfellhernienrezidiv) trat in 24 Fällen (7.4%) auf, eine isolierte Hiatushernie in acht (2.5%) und ein kombiniertes Rezidiv in sechs (1.8%). Insgesamt wurden 38 Rezidive diagnostiziert (11.7%), davon 19 bei 131 überlebenden ECMO-Patienten (14.5%). Nach Primärverschluss lag die Rezidivrate bei 8.8% (6/68 Patienten) und bei 12.7% nach Zwerchfellrekonstruktion mit einem Kegelpatch (32/251 Patienten). Nach Einteilung gemäß der Defektgröße konnten höhere Rezidivraten bei größeren Defekten nachgewiesen werden (Defektgröße A 0%, Defektgröße B 2.8%, Defektgröße C 13.1%, Defektgröße D 37.5%).
Rezidive nach Korrektur einer angeborenen Zwerchfellhernie wurden innerhalb von 12 Monaten postoperativ in 21 Fällen (55.3%) und innerhalb von 24 Monaten in 32 Fällen (84.2%) nachgewiesen.

Die chirurgische Technik zur Zwerchfellrekonstruktion bei angeborener Zwerchfellhernie hat einen hochgradigen Einfluss auf die Langzeit-Ergebnisse. Mit Verwendung eines kegelförmigen Goretex®-Patches konnte eine Langzeit-Rezidivrate von 12.7% nach offener Operation innerhalb einer Nachbeobachtungszeit von minimal zwei und maximal 10 Jahren erreicht werden. Als unabhängige Einflussgrößen auf die Rezidivrate nach operativer Korrektur einer angeborenen Zwerchfellhernie konnten ein linksseitiger Zwerchfelldefekt und die Notwendigkeit der Implantation eines Bauchdeckenpatches identifiziert werden. Bei linksseitigem Zwerchfelldefekt galt dies auch für eine intrathorakale Lage der Leber.
Es ist essentiell notwendig, diese Patienten im Rahmen eines langzeitigen Nachsorgeprogrammes mit regelmäßigem Röntgen nachzuuntersuchen – da die meisten Kinder mit Zwerchfellhernien-Rezidiv keine oder kaum klinische Symptome hatten (97.4%) und da 44.7% der Rezidive erst nach dem 1. Lebensjahr auftraten. Nur ein strukturiertes Nachsorgeprogramm mit regelmäßiger radiologischer Bildgebung aller überlebenden Kinder mit Zwerchfellhernie erlaubt ein verlässliches Erkennen von Rezidiven. Werden Patienten nur bei Symptomen radiologisch kontrolliert, wird die große Mehrheit nicht diagnostiziert und es besteht das Risiko der akuten Darminkarzeration, Darmgangrän und letalen Septikämie.

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PUBLICATIONS OF RESULTS OF THIS THESIS

Article:

Zahn, K., Schaible, T., Rafat, N., Weis, M., Weiss, C., Wessel, L. (2021). **Longitudinal Follow-Up With Radiologic Screening for Recurrence and Secondary Hiatal Hernia in Neonates With Open Repair of Congenital Diaphragmatic Hernia—A Large Prospective, Observational Cohort Study at One Referral Center.** Front. Pediatr. 9:796478, doi: 10.3389/fped.2021.796478

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Wessel LM and Zahn K (2019). **Kinderchirurgie, Viszerale und allgemeine Chirurgie des Kindesalters. Kapitel 34: Kongenitale Zwerchfellhernie; 295-317.** 3. Auflage, Springer Reference Medizin.

Oral presentations at national and international congresses:

‚Update chirurgisches Management der kongenitalen Zwerchfellhernie – Update surgical management of congenital diaphragmatic hernia (CDH)', 47. Jahrestagung der GNPI, 16.-19.06.2021, diigital

‚Longitudinal follow-up with radiologic imaging is essential to reliably detect recurrence in patients with CDH', CDH-Symposium 2020, Houston (Texas), USA

‚Die chirurgische Zwerchfellhernienrekonstruktion: verschiedene Möglichkeiten und Langzeitprognose bezüglich Rezidiv und Darmverschluß', 1. CDH-Familienseminar des Vereins 'Zwerchfellhernie bei Neugeborenen', 28th -29th july 2018, Wernau (Germany)

‚Identification of risk-factors for recurrence after neonatal repair of congenital diaphragmatic hernia – a prospective cohort-study', Congenital Diaphragmatic Hernia – International Workshop Symposium, 14th-15th november 2017, Liverpool (UK)

‚Enhancing restoring abdominal viscera in repair of large congenital diaphragmatic hernia by the use of a cone-shaped patch', Congenital Diaphragmatic Hernia Experts Forum (STEPS teaching seminar), 1st-2nd september 2017, Madrid (Spanien)

‚Varianten des offenen Zwerchfellhernien-Verschlusses', 112. Jahrestagung der Deutschen Gesellschaft für Kinder- und Jugendmedizin (DGKJ), 14th-17th september 2016, Hamburg (Germany)

‚10 Jahre Kegelpatch in der operativen Versorgung von Neugeborenen mit kongenitaler Zwerchfellhernie – signifikante Senkung der Rezidivrate', 133. Kongress der Deutschen Gesellschaft für Chirurgie, 26th-29th april 2016, Berlin (Germany)

Poster presentations at national and international congresses:

‚Identification of risk-factors for recurrence after neonatal open repair of congenital diaphragmatic hernia (CDH) – a prospective cohort-study ', 18. EUPSA-Kongress, 17th-20th may 2017, Limassol (Zypern)

‚Establishment of a longitudinal and multidisciplinary follow-up program for neonates with Congenital Diaphragmatic Hernia allows an evaluation of new surgical approaches', 19. Chirurgische Forschungstage 08th-10th october 2015, Würzburg (Germany)

‚10-year experience with the cone-shaped patch in surgical correction of neonates with congenital diaphragmatic hernia', International Workshop on Congenital Diaphragmatic Hernia, 14th-15th september 2015, Toronto (Kanada)

10 CURRICULUM VITAE

PERSONAL DATA

Name and first name:	Katrin Bettina Zahn
Date of birth:	21.12.1975
Place of birth:	Bochum, Germany

PROFESSIONAL CAREER

since 04.2017	certified fellow of the European Acadamy of Paediatric Urology (FEAPU)
since 01.10.2015	senior consultant of Paediatric Urology, Department of Paediatric, Adolescent and Reconstructive Urology, UMM Mannheim, Prof. Dr. R. Stein
since 01.02.2012	senior consultant, Department of Paediatric Surgery, UMM Manheim, Prof. Dr. Dr. h.c. L.M. Wessel
24.06.2010	certified paediatric surgeon
01.10.2004	licence to practice medicine (Approbation)
2003-2010	training in paediatric surgery, Department of Paediatric Surgery, UMM Mannheim (2003-2008 Prof. Dr. K.L. Waag, since 09/2008 Prof. Dr. Dr. h.c. L.M. Wessel)

UNIVERSITY

1995-2002	medical studies at Christian-Albrechts-Universität Kiel
21.10.2002	third exam (3. Staatsexamen)
20.03.2001	second exam (2. Staatsexamen)
31.08.1999	first exam (1. Staatsexamen)
13.03.1998	preclinical exam (Physikum)

SCHOOL

12.06.1995	graduation (Abitur)
1986-1995	high-school: Schiller-Schule, Bochum
1982-1986	elementary school: Gräfin-Imma-Grundschule, Bochum

11 DANKSAGUNG

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mich immer wieder freundlich erinnert, von neuem motiviert und
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Geduld ist ein Baum mit bitteren Wurzeln,
der süße Früchte trägt.

Sprichwort aus Persien