From the Fetal Treatment Center

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Aus der Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe - Großhadern

der Ludwig-Maximilians-Universität München, Deutschland

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Congenital cystic adenomatoid malformation of the lung (CCAM) and Bronchopulmonary sequestration (BPS): Prenatal diagnosis, pre- and postnatal interventions, and early- and long-term outcome (14 years clinical experience with 60 patients)

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„Über sieben Brücken musst du geh'n …“, Song

Kongenitale zystisch-adenomatoide Malformation der Lunge (CCAM) und Bronchopulmonale Sequestration (BPS): Pränatale Diagnose, prä- und postnatale Interventionen, sowie Früh- und Langzeitverlauf (14 Jahre klinische Erfahrung mit 60 Patienten)

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List of abbreviations

&	And
@	At
A	Ascites
AFP	Alpha-fetoprotein
ANOVA	Analysis of variance
BA	Bronchial atresia
BC	Bronchogenic cyst
BE	Bronchiectasis
Bilat.	Bilateral
BPS	Bronchopulmonary sequestration
BS	Bronchial stenosis
CCAM	Congenital cystic adenomatoid malformation of the lung
CDH	Congenital diaphragmatic hernia
CHOP	Children's Hospital of Philadelphia
ci	Contraindication
CLE	Congenital lobar emphysema
cm	Centimeter
CT	Computed tomography
CVR	CCAM volume ratio
d. h.	Das heißt (deutsche Abkürzung)
DOL	Day of life (old)
E	Subcutaneous edema
ECMO	Extracorporeal membrane oxygenation
excl.	Excluding
EXIT	*Ex utero* intrapartum treatment
F/u	Follow-up
g	Gram
GA	Gestational age
GERD	Gastro-esophageal reflux disease
HFOV	High-frequency oscillatory ventilation
Hydrothx	Hydrothorax
ICU	Intensive care unit
ID	Infant death
i. e.	That is
incl.	Including
Info	Information
IUD	Intrauterine death
L	Left side
L/T	Lung to thorax ratio
LLL	Left lower lobectomy
LMP	Last menstrual period
LMU	Ludwig-Maximilians-Universität
LUL	Left upper lobectomy
Med. Shift	Mediastinal shift

mo	Month(s) old
mod.	Moderate
MRI	Magnetic resonance imaging
MTR	Mass to thorax ratio
n/a	Not available, not applicable, not accessible
ND	Neonatal death
No.	Number (case number or study number)
Oligo	Oligohydramnios
P	Pleural effusion
Periop.	Perioperative
Poly	Polyhydramnios
PPHN	Persistent pulmonary hypertension of the newborn
PPV	Positive predictive value
PROM	Premature rupture of membranes
PTL	Preterm labor
R	Right side
Ref.	Reference
RLL	Right lower lobectomy
RML	Right middle lobectomy
RP	Right pneumonectomy
S/P	Status post
SSW	Schwangerschaftswoche(n) (deutsche Abkürzung); Beispiel: 25+6 SSW = 25 Wochen + 6 Tage andauernde Schwangerschaft = 25.9 gestational weeks
TAE	Transcatheter arterial embolization
TGA	Transposition of the great arteries
TOP	Termination of pregnancy
UCSF	University of California, San Francisco
unkn.	Unknown
US	Ultrasound
USA	United States of America
wks	Gestational weeks
yo	Year(s) old

TEIL I

Die sonographische Überwachung der pränatalen Tumorgröße und eine fetale Therapie wirken einer möglichen Hydropsentwicklung entgegen und verbessern den Frühverlauf von CCAM und BPS mit gutem Langzeitergebnis

PART I

Prenatal ultrasonographic tumor size monitoring and fetal therapy prevent potential hydrops development and enhance the early outcome of CCAM and BPS with a favorable long-term outcome

1. Zusammenfassung Teil I

Fetale zystische Lungenläsionen, wie die kongenitale zystisch-adenomatoide Malformation der Lunge („congenital cystic adenomatoid malformation of the lung“, CCAM) und die bronchopulmonale Sequestration („bronchopulmonary sequestration“, BPS), galten früher als seltene und prognostisch ungünstig verlaufende Erkrankungen. Als in den letzten 20 Jahren immer mehr zystische Lungenläsionen vor der Geburt mittels Ultraschall entdeckt wurden, konnte der Beweis angetreten werden, dass der perinatale Verlauf viel vorteilhafter war als zuvor angenommen. Die Schwere der Erkrankung war in früher publizierten Studien, aufgrund der weit verbreiteten Praxis der Schwangerschaftsunterbrechungen und der selektiven Auswahl der am schwersten erkrankten Feten, überbewertet worden. Neuere klinische Untersuchungen weisen einen günstigen perinatalen Verlauf nach (für entsprechende Literaturangaben siehe dritter Absatz der INTRODUCTION). Ungeachtet dieser Tatsache gibt es kaum Langzeitstudien, und die pränatalen prognostischen Einflussgrößen werden immer noch kontrovers und häufig wenig detailliert diskutiert. Eine angemessene Beratung werdender Eltern und die Entscheidungsfindung für das therapeutische Vorgehen sind hierdurch erschwert. Deshalb führte ich eine Langzeitverlaufsstudie an einer großen Zahl pränatal diagnostizierter Kinder mit fetalen zystischen Lungenläsionen, an zwei großen medizinischen Versorgungszentren, durch. Ich verglich den perinatalen Verlauf der Kinder mit dem langzeitlichen Verlauf. Um die pränatalen prognostischen Einflussgrößen für den perinatalen und den langzeitlichen Verlauf identifizieren zu können, untersuchte ich die Daten der pränatalen Ultraschallbilder der Kinder. Der prognostische Wert jedes einzelnen pränatalen Parameters, der in dieser Studie untersucht wurde, wurde mit den

bisher publizierten prognostischen Aussagen verglichen, die ich durch eine zusätzliche statistische Analyse aller Patienten aus den in der Literatur veröffentlichten großen Studien gewann. Aufgrund der Ergebnisse dieser Studie und aufgrund der Erfahrungen der Spezialisten am Medizinischen Versorgungszentrum der Universität von Kalifornien in San Francisco („University of California, San Francisco“, UCSF), USA, und am Klinikum Großhadern der Ludwig-Maximilians-Universität (LMU) München, Deutschland, konnten eindeutige Strategien für die Diagnostik und Therapie der fetalen zystischen Lungenläsionen formuliert werden.

Um den Krankheitsverlauf von Kindern mit fetalen zystischen Lungenläsionen und die Prädiktoren für den Verlauf zu untersuchen, wendete ich folgende Methoden an: Zuerst wurde ein eigens zu diesem Zweck entwickelter Fragebogen mit 39 Fragen an die Eltern verschickt, deren Kinder zwischen 1988 und 2002 am Medizinischen Versorgungszentrum der UCSF und am Klinikum Großhadern der LMU München, wegen einer pränatal diagnostizierten zystischen Lungenläsion, sonographisch evaluiert worden waren. Das Patientenkollektiv bestand sowohl aus den an diesen zwei tertiären Versorgungszentren behandelten Patienten als auch aus Patienten, die an den beiden Zentren beraten wurden, aber in sekundären oder primären Versorgungszentren behandelt wurden. Anschließend wertete ich die pränatalen Ultraschallbilder und/oder Ultraschallbefundberichte derjenigen Patienten aus, deren Eltern auf die Anfrage hin antworteten. Daten über die Größe und den Typ sowie über die Lage der zystischen Lungenläsion und das Auftreten oder Ausbleiben eines fetalen Hydrops wurden extrahiert. Auch die Entwicklung und Ausdehnung von mediastinaler Verschiebung, Aszites, Pleuraergüssen, Perikardergüssen, Hautödemen, Plazentahypertrophie und

Polyhydramnion sowie das fetale Wachstum untersuchte ich anhand der Daten. Die Größe der Tumormasse wurde als (i) klein, (ii) mittel, (iii) groß oder (iv) sehr groß eingestuft. Die anderen quantifizierbaren Ultraschallparameter wurden als (i) nicht vorhanden, (ii) mild, (iii) moderat oder (iv) ausgeprägt klassifiziert. Schließlich wertete ich die beantworteten Fragebögen und sämtliche Krankengeschichten der Patienten hinsichtlich des Krankheitsverlaufes in der Schwangerschaft, in der Neonatalperiode und in der Kindheit aus. Klinische Daten über gegenwärtige und frühere respiratorische und nicht-respiratorische Symptome, therapeutische Interventionen und Operationen, bildgebende Untersuchungen und perinatale Diagnostik sowie demographische Daten wurden entnommen. Alle postnatalen Verlaufsdaten wurden dann in (i) frühe Verlaufsdaten der Neonatalperiode, (ii) zwischenzeitliche Daten über den Verlauf in der Kindheit und (iii) abschließende Daten über den endgültigen Ausgang gruppiert. Ich bestimmte das Alter, in dem Symptomverbesserungen von respiratorischen und nicht-respiratorischen Symptomen auftraten. Atemwegsbeschwerden, wie zum Beispiel asthmatische Symptome, rezidivierende Atemwegsinfektionen und Beatmungspflichtigkeit, wurden entsprechend ihres Schweregrades in vier Gruppen eingeteilt: (i) keine, (ii) milde, (iii) mäßige oder (iv) schwerwiegende respiratorische Symptome. Diese Studie stellte die klinisch relevanten respiratorischen Symptome in den Mittelpunkt der Untersuchung. Am Medizinischen Versorgungszentrum der UCSF und am Klinikum Großhadern der LMU München wurde keine Lungenventilations- oder -perfusionsszintigraphie zur Erfassung von subtileren Lungenfunktionsstörungen durchgeführt. Die Patienten der Studie wurden in fünf chirurgische Interventionsgruppen eingeordnet: (1) Schwangerschaftsunterbrechungen, (2) invasive Fetaltherapie, (3)

Neugeborenenchirurgie, (4) Kinderchirurgie und (5) keine chirurgischen Interventionen. Postoperative frühe Komplikationen (sofern sie einen verlängerten Krankenhausaufenthalt nötig machten) und späte Beeinträchtigungen (z.B. starke Narbenbildung oder Pectus excavatum) sowie andere nicht-respiratorische Anomalien wurden recherchiert – insofern sie auftraten. Alle Daten wurden mit den folgenden statistischen Methoden ausgewertet: Chi-Quadrat-Test nach Pearson, *t*-Tests der Mittelwerte, Varianzanalyse („analysis of variance“, ANOVA) und bivariate Korrelation.

Die Resultate der Studie lauten wie folgt: Es wurden 182 Elternfragebögen versandt mit einer Rücklaufquote von 34,6%. Sechzig Kinder im Durchschnittsalter von 5,9 Jahren (Maximalalter war 13,1 Jahre) wurden in diese Studie über den Langzeitverlauf von Feten mit zystischen Lungenläsionen aufgenommen. Von diesen 60 Kindern mussten 13 (22%) nicht operiert werden, 15 (25%) wurden im Kindesalter operiert, 12 (20%) wurden in der Neonatalperiode operiert, 14 (23%) hatten invasive Fetaltherapie (dazu gehörten 3 verstorbene Fälle), 4 (7%) der Schwangerschaften wurden unterbrochen und 2 (3%) Feten waren Frühgeburten und überlebten, aufgrund mütterlicher Kontraindikationen gegen eine fetale invasive Therapie, nicht. Die Überlebensrate war 94% (51 von 54 Fällen), und zwar unter Ausschluss der vier Schwangerschaftsunterbrechungen und der zwei verstorbenen unbehandelten Fälle, bei denen eine Fetaltherapie indiziert gewesen wäre. Nach der Geburt zeigten 31 (61%) von den 51 lebenden Kindern keine Symptome oder nur eine milde respiratorische Anfangssymptomatik. Mäßige Atembeschwerden hatten 4 (8%) Neugeborene, 16 (31%) hatten schwerwiegende anfängliche Atembeschwerden. Gewöhnlich aber lösten sich die frühen respiratorischen Symptome in der Neonatalperiode (41%) oder in den ersten

beiden Lebensjahren (34%) auf, selten auch erst im vierten Lebensjahr (16%). Nur 3 (9%) Kinder behielten mäßige Symptome bei. Bei der letzten Verlaufskontrolle waren 48 (94%) von den 51 lebenden Kindern asymptomatisch (38 Fälle) oder hatten nur ganz milde respiratorische Symptome (10 Fälle). Der endgültige respiratorische Verlauf war somit unabhängig vom anfänglichen Krankheitsverlauf. Bei näherer Untersuchung des anfänglichen Krankheitsverlaufes fiel auf, dass die Kinder umso eher operiert wurden, je schwerer ihre anfänglichen Atembeschwerden waren (Signifikanzniveau von $p<0,001$). Das spiegelte sich auch in der Zugehörigkeit zu einer der fünf Interventionsgruppen wider. Je schwerer die anfänglichen Atembeschwerden waren, desto niedriger war auch das Gestationsalter der Kinder bei der Geburt ($p<0,001$). Es wurden 19 (37%) der 51 lebenden Kinder zu früh geboren (zwischen 25+6 und 37+3 Schwangerschaftswochen (SSW)). Von diesen 19 frühgeborenen Kindern waren 9 Kinder in der Fetalperiode operiert worden, 8 von diesen 9 hatten schwerwiegende anfängliche Atembeschwerden. Die Frühgeburtlichkeit war zusätzlich mit vorübergehenden, perinatalen nicht-respiratorischen Komplikationen und auch mit anhaltenden Schwierigkeiten bei der Nahrungsaufnahme und der Gewichtszunahme verbunden. Diese Schwierigkeiten ließen alle im Alter von etwa zwei Jahren nach. Postoperative Spätkomplikationen waren starke Narbenbildung oder die Ausbildung eines Pectus excavatum oder beides zusammen. Diese Komplikationen traten bei 8 (21%) von 38 überlebenden operierten Kindern auf. Weitere kongenitale Anomalien traten in 5 der 60 untersuchten Patienten auf: Albinismus, Asperger-Syndrom, Kraniosynostose, Mayer-Rokitansky-Küster-Hauser-Syndrom und Dysplasie der Olivenkerne. Nur in zwei dieser fünf Fälle war eine pränatale Diagnose der zusätzlichen Anomalie sonographisch möglich. Die zystischen

Lungenläsionen der Kinder wurden pränatal im Durchschnitt mit 20+5 ± 3+6 SSW diagnostiziert und sonographisch als CCAM (in 51 Fällen), BPS (in 5 Fällen) und CCAM-BPS-Hybrid (in 4 Fällen) erkannt. In 50 Fällen wurden diese Läsionen als Stocker-Typ I (12 Fälle), Typ II (17 Fälle) und Typ III (21 Fälle) klassifiziert. Die fetalen zystischen Lungentumoren waren schlussendlich sehr groß (18 Fälle), groß (8 Fälle), mittelgroß (14 Fälle) und klein (13 Fälle) geworden; 7 Tumormassen verschwanden sonographisch ganz. Während der Schwangerschaft waren 25% der Tumoren größer geworden, 35% behielten dieselbe relative Größe bei und 40% wurden kleiner. Die meisten anfänglich sehr großen Tumoren blieben sehr groß (10 Fälle), und auch die meisten der anfangs kleinen Tumoren blieben klein oder verschwanden sonographisch (8 Fälle). Tumoren, die während der Fetalzeit zu einem beliebigen Zeitpunkt groß oder sehr groß wurden, hatten sich im Durchschnitt während 22+2 ± 1+4 SSW vergrößert. Nahm die Größe der (sehr) großen Tumoren jedoch wieder ab, so geschah dies durchschnittlich mit 27+4 ± 3+5 SSW. Im Vergleich dazu vergrößerten und/oder verkleinerten sich die in der Maximalgröße nur klein oder mittelgroß gebliebenen Tumoren im Durchschnitt ungefähr 1+4 SSW und/oder 3+0 SSW später, d.h. mit 23+6 ± 2+1 SSW und/oder 30+4 ± 3+6 SSW. Das Ausmaß der Mediastinalverschiebung folgte der Größe und dem Wachstumsverlauf der Tumormasse. Ein fetaler Hydrops bildete sich in einer kritischen Phase zwischen 18+3 SSW und 28+3 SSW (23+0 ± 3+1 SSW im Durchschnitt) bei 13 Feten (22% der 60 Patienten) mit sehr großen Tumoren aus. Eine Rückbildung des Hydrops erfolgte nach fetaler Tumorresektion in allen fünf fetal-operierten Überlebenden nach 1 bis 3 Woche(n). Eine große Tumor-Endgröße, ein hoher Grad an mediastinaler Verschiebung und das Auftreten eines Hydrops waren die wichtigsten

Prognoseprädiktoren ($p<0,001$ bis $p<0,01$) für einen anfänglich komplizierten Verlauf mit Frühgeburtlichkeit und respiratorischen Frühsymptomen. Diese Frühsymptome erforderten pränatale und/oder postnatale therapeutische Interventionen wie Tumorentfernung, Beatmung und Intensivtherapie. Drei der klassischen Symptome eines fetalen Hydrops (gemäß Definition nach Evans, 1996) waren in dieser Studie, wie folgt, tatsächlich signifikant mit einem Hydrops verknüpft: Hautödeme, Aszites und Pleuraergüsse. Aber auch die Plazentahypertrophie und das Polyhydramnion waren zwei weitere Symptome, die mit einem fetalen Hydrops signifikant assoziiert waren. Drei dieser Hydrops-assoziierten Symptome, nämlich Hautödeme, ausgeprägter Aszites und Plazentahypertrophie, waren außerdem in der statistischen Berechnung – unabhängig voneinander – signifikant mit der Größe der Tumormasse und dem frühen respiratorischen Verlauf verknüpft. Pleuraergüsse und Polyhydramnion waren zwar hinsichtlich der Tumorgröße prognostisch aussagekräftig, konnten jedoch den frühen respiratorischen Verlauf nur unbeständig und nicht unabhängig von den anderen Hydrops-assoziierten Symptomen vorhersagen. Perikardergüsse waren weder mit der Entwicklung eines Hydrops noch mit der Tumorgröße und auch nicht mit dem frühen respiratorischen Verlauf assoziiert. Eine potenziell prognostische Einflussgröße hinsichtlich der Tumorgröße und des respiratorischen Frühverlaufes aber war der Stocker-Typ der zystischen Lungenläsion, da solide erscheinende Tumoren vom Stocker-Typ III häufiger zur Regression tendierten und einen besseren Verlauf zeigten, als Stocker-Typ I Tumoren mit sich rasch füllenden, dominanten Zysten. Der frühe respiratorische Krankheitsverlauf, der mit unterschiedlich schweren Symptomen einherging, war mit den zuvor diskutierten, pränatalen Parametern vorhersagbar. Im

Unterschied zum frühen respiratorischen Krankheitsverlauf zeichnete sich der respiratorische Langzeitverlauf durch einen (bis auf wenige Ausnahmen) einheitlich vorteilhaften Verlauf aus. Damit war der Langzeitverlauf unabhängig von den pränatalen Prädiktoren ($p>0,3$). Bei der letzten Nachuntersuchung waren 94% der Kinder (48 der 51 lebenden Kinder) im Durchschnittsalter von 5,9 Jahren bei guter Gesundheit, und das ist ein exzellentes Langzeitergebnis.

Fazit der Studie ist, dass die Größe des fetalen zystischen Lungentumors der Dreh- und Angelpunkt im Hinblick auf den antenatalen, perinatalen, frühen und zwischenzeitlichen respiratorischen Verlauf der Kinder ist. Die Tumorgröße beeinflusst alle anderen fetalen Symptome. Feten mit sehr großen Tumoren haben ein hohes Risiko, einen Hydrops zu entwickeln. Der Hydrops ist ein alarmierender und lebensbedrohlicher Zustand. Maßangaben der Tumorgröße wie die CCAM-Volumen-Ratio (CVR), die Masse-zu-Thorax-Ratio (MTR) oder auch die Lungen-zu-Thorax-Ratio (L/T) tragen zur Identifizierung der durch Hydropsbildung gefährdeten Feten bei. Die statistische Analyse der Patientendaten dieser Studie zeigt, dass die Tumorendgröße und die Entwicklung eines Hydrops die stärksten Prädiktoren für den anfänglichen Krankheitsverlauf sind. Dies wird auch durch die Resultate der Auswertungen der Daten aller veröffentlichten größeren Patientenserien untermauert. Zweitrangige prognostische Einflussgrößen sind einzelne Tumor-assoziierte und Hydrops-assoziierte Symptome wie eine höhergradige Mediastinalverschiebung, ein ausgeprägter Aszites und eine Plazentahypertrophie. Demgegenüber zeigen sich milde seröse Ergüsse und das isolierte Polyhydramnion häufig nur vorübergehend und haben, wenn sie unabhängig von den anderen fetalen Symptomen auftreten, keinen prognostischen Aussagewert für die Krankheit.

Eine engmaschige sonographische Überwachung von Feten mit zystischen Lungentumoren sollte stattfinden, zumindest während der kritischen Phase des potentiellen Tumorwachstums und der möglichen Hydropsentwicklung zwischen der 19. und 29. SSW. Die Früherkennung von ersten Hydropsanzeichen ist entscheidend für das rechtzeitige fetaltherapeutische Eingreifen. Unverzügliche fetaltherapeutische Interventionen erhöhen die Überlebenschancen für hydropische Feten. Todesfälle kommen fast ausschließlich bei verspäteter Fetaltherapie und weit fortgeschrittenem Hydrops vor. Einige Chirurgen befürworten sogar an nicht-hydropischen Feten zu operieren, wenn diese sehr große Tumoren haben, um der Entwicklung einer pulmonalen Hypoplasie vorzubeugen. Diese Vorgehensweise bedarf weiterer Untersuchungen. Etablierte fetalchirurgische Verfahren bei zystischen Lungentumoren sind die (serielle) Aspiration oder Shunt-Einlage, die der Drainage von sich rasch vergrößernden Zysten oder Spannungshydrothoraxen dient, und die offene Fetalchirurgie zur Resektion von sehr großen Tumoren. Die fetalchirurgischen Eingriffe führen in 55 bis 78% der Fälle zum Erfolg. Das bedeutet, dass sich der Hydrops in der ersten bis dritten Woche nach der Operation wieder zurückbildet und das Kind überlebt. Zur Linderung der Symptome bei einem massiven Polyhydramnion oder bei einem massiven Aszites kann die (serielle) Amniozentese oder Parazentese zur Anwendung kommen. Der Nutzen anderer minimal-invasiver, alternativer Verfahren, wie die vaskuläre Embolisation und die Gabe von Steroiden, werden zurzeit untersucht. Ist der Fetus, der durch eine Hydropsentwicklung bedroht wird, älter als 32 SSW, so ist die sofortige Entbindung per Kaiserschnitt mit anschließender Operation des Neugeborenen der invasiven Fetaltherapie vorzuziehen. Unmittelbare postnatale Behandlungsmöglichkeiten, wie die *ex utero* intrapartum

Therapie (EXIT), die extrakorporale Membranoxygenation („extracorporeal membrane oxygenation“, ECMO) und die hochfrequente oszillatorische Ventilation (HFOV), verbessern die Prognose der ernsthaft betroffenen Feten nach der 32. SSW. Im weiteren Verlauf nach der Geburt sollte man zu einer möglichst frühzeitigen Entfernung des radiologisch nachgewiesenen Tumors raten. Diese Strategie hat sich auch bei asymptomatischen Kindern bewährt. Die Tumorentfernung beugt einer möglichen Entstehung von Atemwegsinfektionen, Pneumothoraxen, Blutungen und einer malignen Transformation des Tumors vor und macht eine sonst lebenslang notwendige Überwachung überflüssig. Neue, minimal-invasive Operationsverfahren sollten berücksichtigt und in der Beratung mit den Eltern der Patienten erwogen werden.

Der Verlauf der Kinder, die pränatal mit fetalen Lungenläsionen diagnostiziert werden, lässt sich wie folgt zusammenfassen: Die reale Mortalitätsrate läge bei nur 7%, wenn moderne pränatale Diagnostik und prä- und postnatale Behandlungsmethoden zur Verfügung stünden und den „hidden survivors“ eine Überlebenschance gegeben würde durch das Unterlassen von Schwangerschaftsabbrüchen. Nur ein Drittel der überlebenden Kinder haben nach der Geburt schwerwiegende respiratorische Symptome. Die Frühgeburtlichkeit hat einen erheblichen Einfluss auf den respiratorischen Frühverlauf, wie auch auf nicht-respiratorische Probleme bei der Ernährung und der Gewichtszunahme. Feten mit sehr großen Tumoren, mit einem Hydrops oder nach fetaltherapeutischen Interventionen haben ein hohes Risiko zu früh geboren zu werden. Sonographische vorgeburtliche Prognoseprädiktoren sind hilfreich bei der Vorhersage des Frühverlaufes. Den Langzeitverlauf können die Prädiktoren jedoch nicht vorhersagen, da die Mehrheit der symptomatischen Kinder aus ihren anfänglichen respiratorischen

Schwierigkeiten, bereits in der Neonatalperiode oder in der frühen Kindheit, herauswächst. Auch die mit der Frühgeburtlichkeit zusammenhängenden nicht-respiratorischen Symptome nehmen mit zunehmendem Alter ab. Seltene, längerfristige respiratorische Symptome sind eine eingeschränkte körperliche Ausdauer, rezidivierende Atemwegsinfektionen und Asthma. Drei der Kinder aus dieser Studie entwickelten solche Symptome. Die anderen 48 überlebenden Kinder waren bei ihrer letzten Nachuntersuchung (im Durchschnittsalter von 5,9 Jahren) frei von klinisch relevanten respiratorischen Symptomen und in ihren alltäglichen Aktivitäten nicht eingeschränkt. Dieses Resultat meiner Studie weist überzeugend darauf hin, dass der Langzeitverlauf von Feten mit zystischen Lungenläsionen, nach adäquater Überwachung und Therapie, hervorragend ist.

2. Summary Part I

Fetal cystic lung lesions, such as congenital cystic adenomatoid malformation of the lung (CCAM) and bronchopulmonary sequestration (BPS), were once considered rare and of poor prognosis. Over the past 20 years as more cystic lung lesions were recognized *in utero* using ultrasound, it became evident that the perinatal outcome was much more favorable than was previously estimated. The seriousness of the disease has been overestimated based on the widespread numbers of terminated pregnancies and the selection of the sickest fetuses in earlier published series. More recent clinical studies provide new evidence of a favorable perinatal outcome (please refer to the references in the third paragraph of the INTRODUCTION). However, hardly any long-term investigation exists and prenatal predictive factors are still controversially debated with a lack of detail. This complicates adequate counseling of expectant parents and management decisions. Therefore, I conducted a long-term follow-up study at two large medical centers on a large number of prenatally diagnosed children with fetal cystic lung lesions. I compared the perinatal outcome with the long-term outcome of the children. To identify prenatal predictive factors for the perinatal and long-term outcome, I reviewed the children's prenatal ultrasound data. The predictive value of each prenatal parameter examined in this study was compared with the published predictions that I obtained from an extended statistical analysis of all major series of patients published in the literature. Based on the findings of this study and the expert knowledge of the fetal treatment specialists at the University of California, San Francisco (UCSF) Medical Center, USA, and at the University Hospital Großhadern of the Ludwig-Maximilians-University (LMU)

Munich, Germany, clear diagnostic and therapeutic strategies for fetuses with cystic lung lesions have been developed.

The following methods to explore the outcome and predictors of children with fetal cystic lung lesions were used: First, I sent a questionnaire with 39 questions (specifically designed for this study) to parents whose children had been prenatally diagnosed with cystic lung lesions and ultrasonographically evaluated from 1988 through 2002 at the UCSF Medical Center and at the University Hospital Großhadern of the LMU Munich. The patient population included patients treated at the two tertiary care centers as well as patients counseled at the two centers, but managed at secondary or primary centers. Second, I reviewed the prenatal ultrasound scans and/or ultrasound reports of the patients whose parents responded to the inquiry. Data about the size, type, and location of the cystic lung lesion and about the presence or absence of a hydrops fetalis were extracted. I also collected information about the development and extension of mediastinal shift, ascites, pleural effusion, pericardial effusion, skin edema, placental thickening, polyhydramnios, and fetal growth. The size of the mass was categorized into (i) small, (ii) moderate, (iii) large, or (iv) very large; the other quantifiable ultrasonographic parameters were classified into (i) not present, (ii) mild, (iii) moderate, or (iv) marked. Finally, based on the returned questionnaires and all medical records, I reviewed the outcome of the pregnancy, the neonatal period, and the childhood of the patients. Clinical data about present and past respiratory and non-respiratory symptoms, therapeutic interventions, surgeries, imaging studies, perinatal diagnostics, and demographic data were extracted. All postnatal outcome data were then grouped into (i) early outcome data of the neonatal period, (ii) interim childhood outcome data, and (iii)

final outcome data. I evaluated the age at improvement of the respiratory and non-respiratory symptoms. Respiratory difficulties such as asthmatic symptoms, recurrent respiratory infections, and the requirement of ventilatory support were categorized into four severity groups with (i) no, (ii) mild, (iii) moderate, or (iv) severe respiratory symptoms. This study focused on the clinically relevant respiratory symptoms. The UCSF Medical Center and the University Hospital Großhadern of the LMU Munich did not perform lung ventilation or perfusion scintigraphy to evaluate more subtle lung function deficits. The study patients were classified into five surgical intervention groups: (1) termination of pregnancy, (2) invasive fetal treatment, (3) neonatal surgery, (4) childhood surgery, and (5) no surgical intervention. If present, postoperative early complications (requiring prolonged hospital stays) and late impairments (e.g. a prominent scar or pectus excavatum) were investigated, as well as other non-respiratory anomalies. All data were analyzed using the following statistical tests: Pearson's chi-square test, *t*-tests of the means, analysis of variance (ANOVA), and bivariate correlation.

The results of the study are presented as follows: 182 questionnaires were sent to the parents, and the response rate was 34.6%. Sixty children at a mean follow-up age of 5.9 years old (maximum 13.1 years) were included in this long-term outcome study of fetuses with cystic lung lesions. Of these 60 children, 13 (22%) did not require surgery, 15 (25%) were operated on in childhood, 12 (20%) were operated on as neonates, 14 (23%) had fetal treatment (including 3 deceased cases), 4 (7%) pregnancies were terminated, and 2 (3%) prematurely delivered fetuses did not survive due to maternal contraindications for invasive fetal treatment. The survival rate was 94% (51 of 54 cases) to the exclusion of the 4 terminated pregnancies and the 2 deceased, untreated fetal

treatment candidates. After birth, 31 (61%) of the 51 surviving children were asymptomatic or had only mild early respiratory symptoms. Moderate respiratory symptoms were present in 4 (8%) neonates, and 16 (31%) had severe early respiratory difficulties. However, the early respiratory symptoms usually resolved in the neonatal period (41%), in the first two years of life (34%), or less frequently, lately until four years of age (16%). Only 3 (9%) children remained with moderate symptoms. At the last follow-up, 48 (94%) of the 51 surviving children were asymptomatic (38 cases) or had only minor respiratory symptoms (10 cases). The final respiratory outcome was independent of the early course of the disease. On closer examination of the early outcome, it became clear that the more severe the children's early respiratory symptoms, the earlier the children received operations (level of significance of $p<0.001$). This is mirrored in the affiliation of the cases to one of the five intervention groups. Moreover, the more severe the early respiratory symptoms were, the lower the gestational age at delivery had been ($p<0.001$). Nineteen (37%) of the 51 surviving children were premature (between 25.9 and 37.4 weeks' gestation). Of these 19 premature children, 9 were fetal treatment patients and 8 of these 9 patients exhibited severe early respiratory symptoms. Prematurity was also associated with transient perinatal non-respiratory complications and prolonged feeding and weight gain difficulties. All of these difficulties improved or disappeared at about two years of age. Late postoperative complications were the development of a prominent scar, a pectus excavatum, or both. These complications occurred in 8 (21%) of the 38 surviving children which had received operations. Additional congenital anomalies were present in 5 of the 60 study patients: albinism, Asperger syndrome, craniosynostosis, Mayer-Rokitansky-Küster-Hauser

syndrome, and olivary nuclei dysplasia. Only in 2 of the 5 cases was a sonographic prenatal diagnosis of the additional anomaly possible. The cystic lung lesions of the children were prenatally diagnosed at a mean gestational age of 20.7 ± 3.8 weeks and sonographically characterized as CCAM (51 cases), BPS (5 cases), and CCAM-BPS-hybrid (4 cases). The lesions were additionally classified as Stocker type I (12 cases), type II (17 cases), and type III (21 cases) in 50 cases. The fetal cystic lung masses finally became very large (18 cases), large (8 cases), moderate (14 cases), and small (13 cases); and 7 masses vanished on sonography. During the pregnancy 25% of the masses had increased, 35% kept the same relative size, and 40% regressed. The majority of the initially very large masses remained very large (10 cases), and most of the initially small masses stayed small or vanished on sonography (8 cases). Masses that had become large or very large at any time point during fetal life had increased during 22.3 ± 1.5 mean gestational weeks. If a (very) large mass subsequently decreased, it occurred at 27.6 ± 3.7 mean gestational weeks. In comparison, masses that had become small or moderate in their maximal size increased and/or decreased about 1.5 and/or 3.0 mean gestational weeks later. The degree of a mediastinal shift followed the size and growth pattern of the mass. A hydrops fetalis developed during a critical period of 18.4 to 28.4 weeks' gestation (mean 23.0 ± 3.2 weeks' gestation) in 13 fetuses with very large masses (22% of the 60 patients). The regression of a hydrops occurred in all five fetal surgery survivors at 1 to 3 weeks after fetal tumor resection. A large final mass size, a high degree of a mediastinal shift, and the development of a hydrops were the most important predictors of the early outcome ($p<0.001$ to $p<0.01$). These predictors were prognostic regarding the development of early respiratory symptoms and complications from prematurity. The

early respiratory symptoms required pre- or postnatal therapeutic interventions or both. Such interventions were a tumor operation, ventilatory support, or intensive care treatment. Three of the following classic hydrops symptoms, as defined by Evans in 1996, were significantly associated with a fetal hydrops in this study: skin edema, ascites, and pleural effusion. Placentomegaly and polyhydramnios were two additional significant fetal hydrops-associated symptoms. Three of these hydrops-associated symptoms, namely skin edema, marked ascites, and placentomegaly, when statistically analyzed, were also, as independent variables, significantly associated with the size of the mass and the early respiratory outcome. Pleural effusion and polyhydramnios were prognostic when the size of the mass was of concern, but these symptoms did not predict the early respiratory outcome consistently and independently of the other hydrops-associated symptoms. A pericardial effusion was neither associated with a hydrops development, nor with the size of the mass or the early respiratory outcome. A potential predictive factor of the mass size and early respiratory outcome was the Stocker type of the cystic lung lesion, as solid appearing Stocker type III lesions tended to regress more often with a better outcome than Stocker type I lesions with dominant rapidly filling cysts. The early respiratory outcome, characterized by different degrees of severity of symptoms, was predictable by the above-discussed prenatal parameters. Unlike the early respiratory outcome, the respiratory long-term outcome was, with a few exceptions, consistently favorable and independent of the prenatal predictors ($p>0.3$). At the last follow-up (at a mean of 5.9 years old), there were 94% of the children (48 of 51 survivors) at good health, and this is an excellent long-term outcome.

In conclusion, the size of the fetal cystic lung tumor is the pivotal point for the antenatal, perinatal, early, and interim respiratory outcomes of the children. The tumor size conditions all other fetal symptoms. Fetuses with very large masses are at high risk of developing a hydrops. A hydrops is an alarming and life-threatening condition. Size measurements, such as the CCAM volume ratio (CVR), the mass to thorax ratio (MTR), or the lung to thorax ratio (L/T), are useful for identifying fetuses at high risk of hydrops development. The statistical analysis of the study data of this thesis proved that the final mass size and development of a hydrops were the strongest predictors of the early outcome. Over and above, the analysis of the data obtained from all major published patient series corroborates these findings. Particular mass size-associated and hydrops-associated symptoms, such as a high degree of a mediastinal shift, marked ascites, and placentomegaly, are secondary prognostic factors. In contrast, solitary polyhydramnios and mild serous effusions are frequently transient. They do not predict the outcome unless combined with other fetal symptoms.

Close ultrasonographic surveillance of fetuses with cystic lung tumors is recommended at least during the critical period of potential mass size increase and hydrops development between 18 and 29 weeks' gestation. The early detection of signs of a hydrops is crucial for initiating timely fetal treatment. Immediate fetal therapeutic interventions increase the chance of survival for hydropic fetuses. Fatalities almost exclusively occur if fetal treatment is delayed and a hydrops becomes advanced. Some surgeons recommend operating even on non-hydropic fetuses with very large masses to prevent pulmonary hypoplasia. This approach needs to be investigated in future studies. Established fetal therapeutic interventions for cystic lung lesions are (serial) aspirations

or shunts to drain rapidly enlarging cysts or tension hydrothoraxes and open fetal surgery to resect very large tumors. Between 55% and 78% of the fetal operations are successful. Success means that the hydrops resolves within 1 to 3 weeks after the operation and the child survives. To relieve the symptoms of an extensive polyhydramnios or an extensive ascites, (serial) amniocenteses or paracenteses can be employed. The benefits of alternative, minimally invasive techniques such as vascular embolization and steroid administration are under investigation. After 32 weeks' gestation, prompt delivery via caesarean section and subsequent neonatal surgery instead of invasive fetal treatment is preferred in hydrops-threatened fetuses. Early postnatal treatment options, such as *ex utero* intrapartum treatment (EXIT), extracorporeal membrane oxygenation (ECMO), and high-frequency oscillatory ventilation (HFOV), improve the outcome of severely affected fetuses post-32 weeks' gestation. Postnatal management recommendations should include the early resection of the radiologically confirmed mass. This strategy is justified even if the child is asymptomatic. Resecting the tumor prevents potential pulmonary infections, pneumothoraxes, bleeding, and malignant transformation of the mass. Thus, it eliminates the need for life-long surveillance. Novel minimally invasive surgery options should be considered and discussed when counseling the patients' parents.

The outcome of children who are prenatally diagnosed with cystic lung lesions can be summarized as follows: The true overall mortality rate can be as low as 7% if modern prenatal diagnostics and pre- and postnatal treatment options are available, and if the "hidden survivors" are given a chance to survive by abandon the practice of terminating pregnancies. Only one-third of the surviving children have severe respiratory symptoms after birth. Prematurity has a considerable influence on the early respiratory

difficulties, as well as on non-respiratory feeding and weight gain problems. Fetuses with very large lesions, with a hydrops, or after fetal therapeutic intervention are at high risk to deliver prematurely. Prenatal ultrasonographic outcome predictors are useful for predicting the early outcome. However, they do not predict the long-term outcome, since the majority of symptomatic children grow out of their initial respiratory symptoms in the neonatal period or during early childhood. Prematurity-associated, non-respiratory symptoms also decrease with increasing age. Rare prolonged respiratory symptoms are limited physical endurance, recurrent pulmonary infections, and asthma. Three of the study patients developed these symptoms. The other 48 surviving children were at their last follow-up (at a mean of 5.9 years old) free of clinically relevant respiratory symptoms and without restrictions in everyday activities. This result of my study convincingly shows that the long-term outcome of adequately monitored and treated fetuses with cystic lung lesions is excellent.

3. Introduction

Congenital cystic adenomatoid malformation of the lung (CCAM) and bronchopulmonary sequestration (BPS) are relatively rare developmental abnormalities of the lung. They are benign lung tumors. The underlying feature of a CCAM is an excessive overgrowth of terminal respiratory bronchioles, forming various sizes of cysts. This abnormal lung tissue is of defective epithelial-mesenchymal architecture. A BPS arises from a supranummary lung bud. It forms non-functioning accessory lung tissue which appears to be of normal epithelial-mesenchymal architecture, but has no connection to the bronchiolar tree. It is supplied by an anomalous systemic artery [3, 104, 123, 125]. These congenital lung lesions are detectable on prenatal ultrasound as solid or cystic masses. Hyperechogenic, solid appearing lesions are indicative for microcystic CCAMs or BPSs. Hypoechoic areas within the mass hint at large cysts, as present in macrocystic CCAMs [24].

Since the first ultrasonographic detection of a CCAM in a fetus in 1975 [55] and a fetal BPS in 1982 [124], fetal chest masses, which were previously considered rare [7, 60, 127], have been reported more frequently after 1990 (Table 6). Recent studies estimate the incidence of CCAM in the range of 1:35000 and 1:10000 births [29, 48, 59, 91, 133]. CCAM is the most common chest mass detected in the fetus and accounts for more than 25% of congenital lung lesions [24, 125]. Less frequent are BPS with 0.15% to 6.6% [32, 63, 130]. Other lung masses, such as lobar emphysema and bronchogenic cyst, have been rarely detected before birth.

In the past, the prognosis of the outcome of fetuses with chest masses was considered to be poor in general [7, 107, 137, 138]. Since the late 1990s, an increasing

number of fetal cystic lung lesions have been detected on sonography, providing new evidence for a favorable outcome [21, 39, 101, 104, 119, 140, 144]. In 1998, Adzick *et al.* [5] researched the outcomes of a large number of fetuses with antenatally detected chest masses and reported 100% survival of non-hydropic fetuses.

Recent studies show that the perinatal outcome of children with CCAM and BPS detected before birth is generally favorable, especially if no signs of non-immune hydrops fetalis (hydrops) develop antenatally. However, most authors address survival before or in the neonatal period as outcome endpoints [5, 34, 59, 91, 143], whereas hardly any study has investigated the long-term outcome of prenatally affected children [81]. The majority of the studies on fetal cystic lung lesions evaluate the prognostic value of prenatal findings. However, attributable to the limited numbers of patients or the lack of detail on the ultrasonographic findings in the published studies, a consensus on the prognostic value of prenatal findings has not been achieved. This research differs from the other studies in its more detailed analysis of the prenatal findings and analysis of a larger patient population, which allowed this study to come to a firmer conclusion.

The goal of this extensive research was four-fold: (1) to study the long-term outcome of children with prenatally detected congenital cystic lung lesions (patients with congenital diaphragmatic hernia were excluded), (2) to compare the long-term outcome with the early outcome of the disease, (3) to determine prenatal ultrasonographic features which are prognostic for short-term and long-term outcomes, and (4) to compare the data of this study with the data obtained by an extended statistical analysis of all major series of patients published in the literature. The new insights in the disease of fetal lung lesions gained through this study add significantly to the improvement of patient counseling.

4. Patients and Methods

4.1 The patients

4.1.1 Fetal patient population at the UCSF Medical Center, USA, and at the University Hospital Großhadern of the LMU Munich, Germany

Between 1988 and 2002 there were 269 cases of fetal cystic lung lesions evaluated and filed at the UCSF Fetal Treatment Center. Of these 269 patients, 130 (48%) had been permanently or temporarily monitored at the UCSF Medical Center using fetal ultrasound. Some of these patients were in critical condition. The remaining 139 (52%) of the 269 patients were not directly monitored at the UCSF Medical Center. Most of these patients were at low risk of clinical deterioration. Their ultrasonographic videotapes and medical records provided by outside institutions were reviewed at the weekly UCSF Fetal Treatment Center meetings and recommendations were given to the referring physicians. Thus, the patient population consisted of patients treated at the UCSF tertiary care center as well as patients treated at outside secondary or primary care centers in the United States of America. During the same time period, 7 patients with fetal cystic lung lesions were evaluated and monitored at the tertiary care center Großhadern of the LMU Munich, Germany. In collaboration with the UCSF Medical Center, I conducted a long-term follow-up study to determine the long-term outcome of patients with fetal cystic lung lesions. The study was approved by the UCSF Committee of Human Research Institutional Review Board (see Appendix).

4.1.2 Recruitment of the fetal study patients

Within the records of the 276 fetal patients evaluated between 1988 and 2002 at the UCSF Medical Center and the University Hospital Großhadern of the LMU Munich, I gathered the contact information of 180 patients from the UCSF Medical Center (180 of 269 patients) and 2 patients from the University Hospital Großhadern of the LMU Munich (2 of 7 patients). Letters were sent to those 182 patients with a known address, soliciting participation in this study. To limit a bias toward the recruitment of favorable outcome patients and patients closely allied with the two participating institutions, I further tried to make contact with all non-responding parents by phone, three weeks after the mailing and with at least three attempts.

4.2 The materials and methods

4.2.1 Long-term follow-up questionnaire

To determine the long-term outcome of children with prenatally detected cystic lung lesions, I developed a follow-up questionnaire with 39 questions (see Appendix). The questions asked about present and past respiratory difficulties, surgeries, imaging studies, other medical problems, general health, and growth of the child. Consenting parents could complete and return the questionnaire by mail in a prepaid envelope that I had sent them with the recruitment letter (see Appendix), or they could answer the questions over the phone.

4.2.2 Medical records review

In addition to the completed questionnaires, all of the patients' medical records were reviewed. The records were filed either at the UCSF Medical Center or at the University Hospital Großhadern of the LMU Munich, or they were sent from outside institutions upon parents' consent, or provided by the patients' parents. The participants' prenatal ultrasound reports or ultrasound scans, as well as their medical records, documenting the patients' perinatal and pediatric outcomes were reviewed.

4.2.3 Prenatal ultrasonographic data

From the participating patients' ultrasound reports I extracted the prenatal ultrasonographic data. When the patients' prenatal ultrasound reports were inconclusive regarding relevant study parameters, Professor Ruth B. Goldstein and I followed up with a review of the ultrasound scans or videotapes.

Ultrasonographic data about the type and diagnosis of the lesion, the size of the mass, the involved thoracic site (right, left, or bilateral), mediastinal shift, hydrops development (with detailed information about ascites, pleural effusion, pericardial effusion, and skin edema), polyhydramnios, placentomegaly, and the size of the fetus (cited as below or above the 90^{th} percentile) were tabulated and labeled with the gestational age at observation (dating based on last menstrual period [LMP]). The quantifiable ultrasonographic parameters were sub-classified into four severity groups (including one group without symptoms, if suitable).

The appearance and type of the mass was categorized into predominantly cystic, solid, or mixed; as well as into type I (cysts >2 cm), type II (cysts <2 cm), or type III (no

cysts identified) – as described by Stocker [125]**.** If the mass was cystic, the size of the largest cyst was recorded (Figure 1).

The mass was categorized into (i) a small sized lesion, if up to one-third of the hemithorax was affected; (ii) a medium sized lesion, if one-third to two-thirds of the hemithorax was occupied; and if the complete hemithorax, or even more than that was affected, it was considered as (iii) large or (iv) very large, respectively (Figures 1 and 2). The mass size was assessed at the initial diagnosis, at its largest stage (maximal mass size), and finally at the end of the pregnancy or before fetal intervention (final/ultimate mass size).

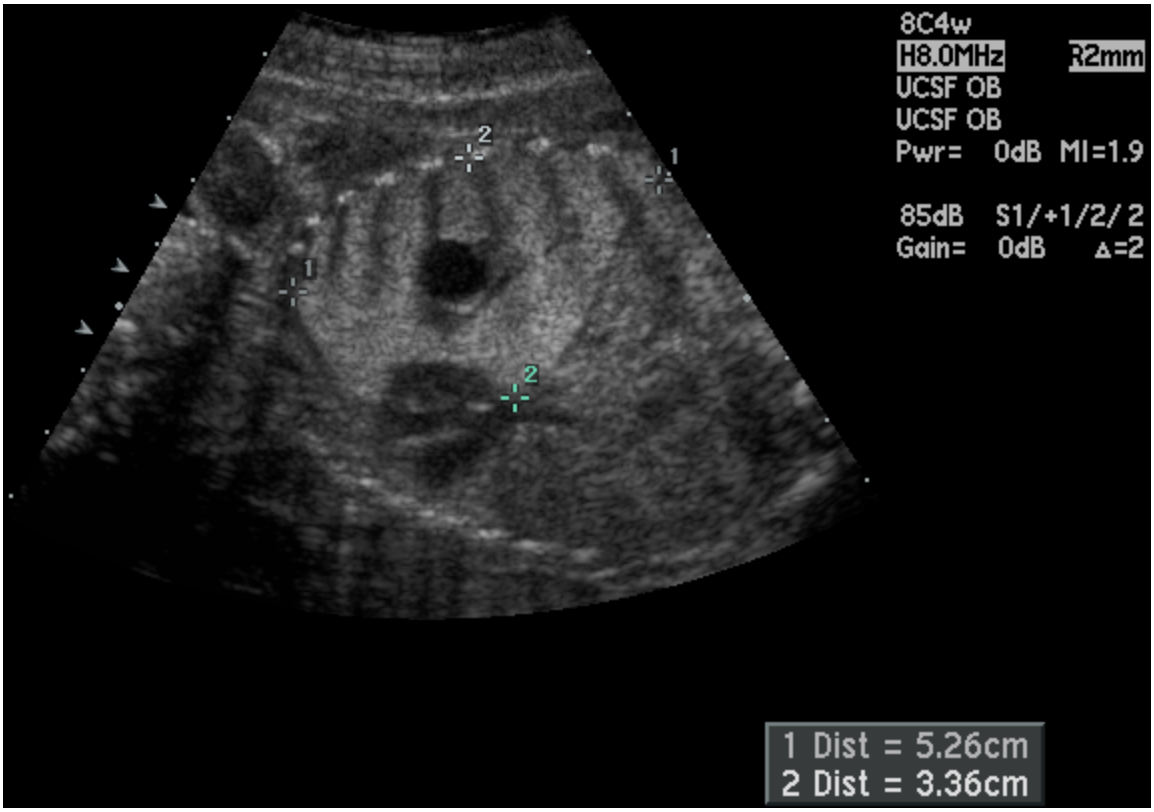


Figure 1. Axial image of the fetal chest at the level of the 4-chamber heart view (case no. 26): At 22 4/7 weeks' gestation, a left-sided CCAM of Stocker type II impresses as a large, solid appearing lung mass with several microcysts (largest microcyst 1.2 cm). Crosses, labeled 1 and 2, show the extent of the tumor.

Figure 2. Longitudinal view of a 22 weeks and 3 days old fetus (case no. 56) with a very large CCAM of Stocker type III: The extremely echogenic lung mass (small arrows) involved almost the whole chest cavity by extending from the right to the left hemithorax and compressing and markedly shifting the fetal heart and mediastinum. The fetus was hydropic with marked scalp edema and ascites (block arrows).

Criteria for the classification of the mediastinal shift were the position of the heart and the ability to visualize the normal contralateral lung tissue. The shift was considered (i) mild, if the fetal cardiac axis was minimally deviated; (ii) moderate, if the heart was considerably shifted to the contralateral side of the thorax, but contralateral lung was still visible; and (iii) marked, if the heart was pressed against the contralateral rib cage, and the contralateral lung was not visible any more (Figure 2).

The extension of ascites, hydrothorax, and pericardial effusion was classified as (i) mild, if little serous cavity fluid was noticeable; (ii) moderate, if fluid accumulation was evident; and (iii) marked, if a large fluid pocket was visible (Figure 2).

Polyhydramnios was considered (i) mild, if the amniotic fluid index (AFI) was >14 cm; (ii) moderate and (iii) marked, if the index was >24 cm and >34 cm, respectively.

Skin edemas were categorized as (i) mild, in the presence of minimal scalp edema (about 2 mm integumentary thickening); as (ii) moderate for increased scalp, or chest wall, or abdominal wall thickening; and as (iii) marked, if severe diffuse skin thickening or anasarca was found (Figure 2).

Placental thickening was called (i) mild, if slightly thickened; (ii) moderate, if the placenta was enlarged more than 3.5 cm; and (iii) marked, if measures of placentomegaly exceeded 5 cm or Maternal Mirror Syndrome was imminent.

A hydrops was defined as an abnormally increased fluid accumulation in two or more serous cavities (ascites, hydrothorax, or pericardial effusion) and/or the presence of skin edema [51]. In addition, cases with marked ascites in combination with polyhydramnios and placentomegaly were also considered hydropic in this study.

If serial ultrasound reports were available, I recorded the progression or regression of the mass size and of the other prenatal symptoms.

4.2.4 Perinatal and pediatric outcome data

The medical records of the study patients were reviewed with a focus on clinical data collected during the prenatal period, the neonatal period, and during the entire baby- and childhood.

I extracted obstetrical history data about parity, karyotype, alpha-fetoprotein (AFP) serum concentration, fertility treatment, mother's age at delivery, and the parents' ethnicity. The following postnatal data about the tumor were collected: the lung lesion's size and its appearance upon radiographic imaging, the size and location (lobe) of the lesion at operation, the type of operation, and the histopathologic diagnosis, outlining the type of the lesion and the cyst sizes.

After reviewing the surgical intervention strategies, I classified the study patients into 5 intervention groups with respect to the invasiveness and the age at the time of the procedure, as follows: (1) the termination of pregnancy (TOP) group; (2) the invasive fetal treatment group, including patients having experienced (a) fetal tumor resection or (b) thoraco-amniotic shunting, cyst aspiration(s), or both; (3) the neonatal surgery group, consisting of patients operated on until 1 month of age; (4) the childhood surgery group, divided into two subgroups, (a) the early childhood operation group with children operated on between 1 to 12 months of age and (b) the late childhood operation group with children operated on after 1 year of age; and finally (5) the no-surgery group.

For all patients I collected the outcome data about respiratory symptoms, presence and duration of ventilatory support, the need for intensive care treatment, and the duration of hospitalization(s). Further, complications after surgery, such as early postoperative problems, final appearance of the thoracic scar, manifestation of a pectus excavatum, and

presence of a residual tumor, were recorded. The 1- and 5-minute Apgar scores, the gestational age at birth, mode of delivery, gender, birth weight, and weight and height at last follow-up were noted.

I grouped the outcome data into (A) the early postnatal outcome (0 to 2 months old), (B) the interim childhood outcome (overall childhood outcome prior to the last follow-up), and (C) the final outcome at last follow-up. As follows, cases were categorized regarding the respiratory outcome as either completely asymptomatic or having mild, moderate, or severe respiratory symptoms (but common transient postoperative symptoms were excluded). In the neonatal period (A), (i) mild symptoms were defined as caused by tachypnea requiring minor blow-by oxygen; (ii) symptomatic moderate cases asked for prolonged oxygen need, limited mechanical respiration for less than 2 days, or both; and (iii) in the severe symptoms category, those patients were placed who had respiratory distress requiring mechanical ventilation for more than 2 days after birth. Respiratory symptoms in childhood (B) and at last follow-up (C) were categorized as (i) mild, if children had minor labored breathing on exertion or mild asthmatic symptoms; (ii) moderate, if they had manifest asthma, frequent pulmonary infections, and/or limited physical endurance; and (iii) severe, if extended re-hospitalizations, prolonged oxygen treatment, or both were required. For each case I included the age at improvement of the symptoms.

Permanent and transient non-respiratory health concerns were also recorded and I classified patients into experiencing (i) no complications; problems being (ii) mild, such as weight gain failure and transient cardiac arrhythmia; problems being (iii) moderate, as

there were prematurity concerns and therapy resistant gastro-esophageal reflux disease (GERD); and (iv) severe ailments, such as congenital syndromes.

4.2.5 Statistical analysis

Using SPSS 11.5 software (SPSS Inc, Chicago, IL, 2002), I performed the following statistical tests: Pearson's chi-square test for categorical or ordinal data, *t*-tests of the means and analysis of variance (ANOVA) for continuous data, and bivariate correlation for both ordinal and continuous data. The results were considered significant at an observed significance level (2-sided P value) of less than 0.05 ($p<0.05$) [72].

5. Results

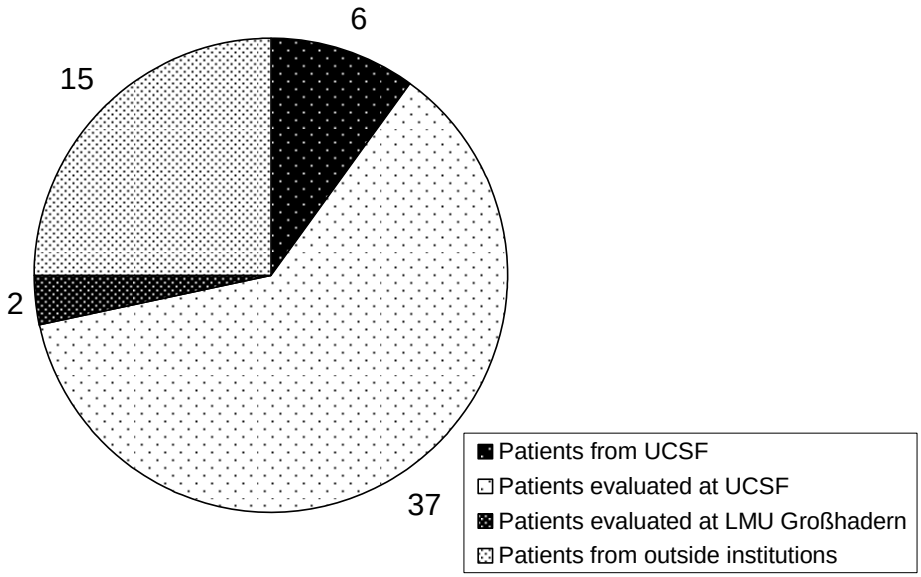
5.1 The patients' response and data source

As a result of two mass mailings and up to three phone call attempts per patient, I reached 63 of 182 families. Herewith the response rate is 34.6%. Sixty (60 of 63) families did consent to participate in the study. They either sent the completed follow-up questionnaire by mail (48 families), or they answered the questions subsequently over the phone (12 families; including the only 2 responding families from the University Hospital Großhadern of the LMU Munich, contacted by Professor Alexander Strauss). Two families did not consent, although both patients were expected to be of good outcome. One family informed me that their fetus had been misdiagnosed as having a fetal lung lesion, and instead it turned out he had a heart disease. The other 119 non-responding families had moved to other locations without leaving further contact information or their addresses, phone numbers, or both were not correct.

From the 60 participating patients, I reviewed 434 prenatal ultrasound reports. In about 10% of the cases, Professor Ruth B. Goldstein and I additionally reviewed the ultrasound scans, because of inconclusive reports regarding relevant study parameters. The scans of the 434 prenatal ultrasound reports had been performed at the UCSF Medical Center (217 ultrasound scans), at the University Hospital Großhadern of the LMU Munich (22 ultrasound scans), and 195 scans had been done at outside institutions in the United States. Six fetuses were diagnosed and monitored at the UCSF Medical Center. Another 39 fetuses had been initially diagnosed at outside institutions, but were finally evaluated or monitored at the UCSF Medical Center (37 patients) or at the

University Hospital Großhadern of the LMU Munich (2 patients). The mean delay until referral after diagnosis was 3.8 ± 3.7 gestational weeks. Of the remaining 15 fetuses, the outside institutions had sent ultrasound scans (as videotapes) and records, and these were discussed at the UCSF Fetal Treatment Center meetings (Figure 3). I also reviewed the records of these meetings.

Figure 3. Study patients (N=60)



I reviewed more than 3,500 pages of the 60 patients' medical records, documenting the patients' perinatal and pediatric outcomes. There were 27 patients delivered and/or operated on at the UCSF Medical Center and 1 patient at the University Hospital Großhadern of the LMU Munich. The remaining 32 patients were born and, if necessary, operated at outside institutions.

5.2 The children's outcomes

5.2.1 The survival rates of the children in the fetal non-intervention groups and in the fetal treatment group were excellent

Of the 60 study fetuses with a completed follow-up, 51 (85%) children were survivors at a mean follow-up of 5.9 ± 3.3 years. They were between 1.3 and 13.1 years old. Of these 51 survivors, 13 children had not received surgery, 12 children were operated on as neonates (1 to 30 days of age), 15 children subsequently underwent surgery in childhood, and fetal interventions were performed in 11 cases. Of the 15 subsequent childhood surgery cases, 11 cases received operations during infancy (at an age of less than 1 year, between 2.4 to 11.7 months of age) and 4 cases received operations later in childhood (between 1.75 to 4.5 years of age). Of the 11 cases treated with fetal intervention, a fetal tumor resection (at 20.4 to 27.7 weeks' gestation) was performed in 7 cases and fetal shunt/cyst aspirations were performed (at 23.1 to 34 weeks' gestation) in 4 cases (Figure 4.1; Tables 2.1, 2.2, and 3).

All 9 (15%) non-survivors were (potential) fetal intervention patients. Three patients (3 of 9 deaths) had fetal treatment with a tumor resection (at 28 to 29.7 weeks' gestation), but died within 2 days after delivery (2 of 3 deaths) and at the age of 2 ½ months (1 of 3 deaths). Two patients (2 of 9 deaths) could not survive because of maternal contraindications for invasive fetal treatment, and they died within hours after preterm spontaneous delivery (at 25.3 to 31.3 weeks' gestation). Four pregnancies (4 of 9 deaths) were terminated (at 22.4 to 25 weeks' gestation) (Figure 4.2, Table 1).

Figure 4.1. Surgical intervention (N=51 survivors)

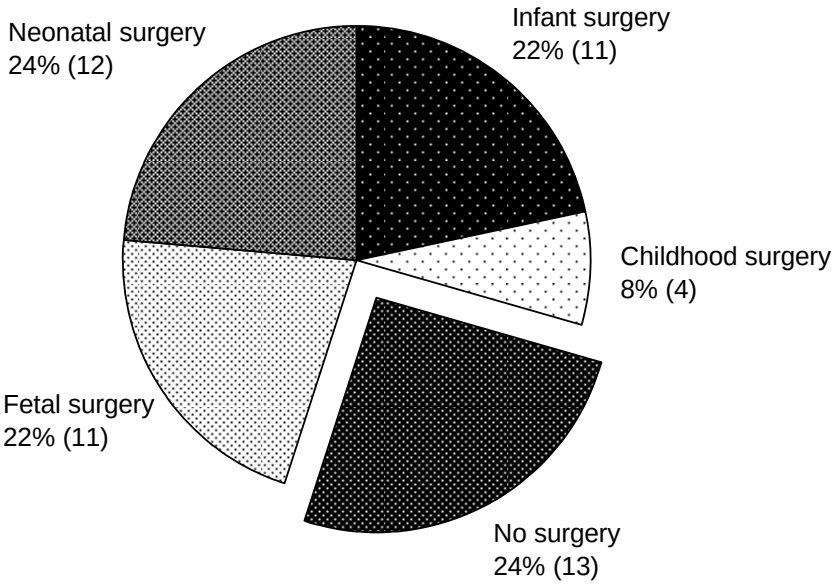


Figure 4.2. Surgical intervention (N=9 non-survivors)

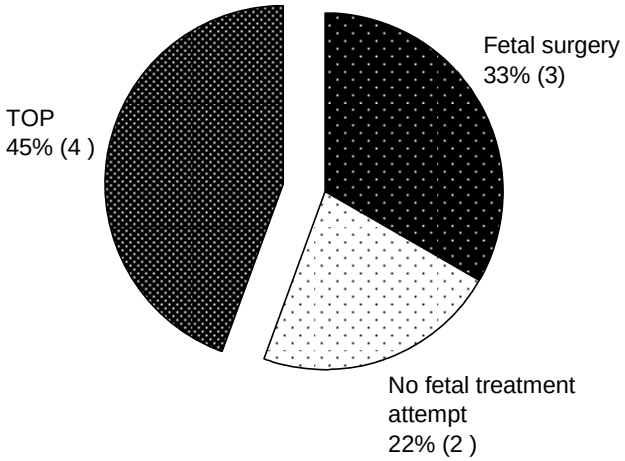


Table 1.
Cause of death in 9 patients with prenatally diagnosed cystic lung lesions

Case no.	Prenatal final mass size	Hydrops fetalis	Intervention group	Age @ birth	Age @ death	Cause of death
49	very large	yes	Fetal surgery @ 29.0 wks	34.0 wks	75 days old	Death after 71 days of ventilation (incl. 10 days ECMO) due to respiratory deterioration (autopsy: resistant pulmonary hypertension, severe cor pulmonale, severe chronic bilateral bronchopulmonary dysplasia, lung baro trauma, pneumonia; prematurity, hydrops, bilat periventricular leucoencephalomalacia; S/P CMV-, candida-, and pseudomonas-sepsis; S/P abdominal bleeding with coagulopathy)
50	very large	yes	Fetal surgery @ 28.0 wks	29.0 wks	2 days old	Death after 2 days of ventilation due to respiratory failure (autopsy: pulmonary hypoplasia, hyaline membrane disease, persistent hydrohemothorax, pulmonary hypertension; prematurity, hydrops)
48	very large	yes	Fetal surgery @ 29.7 wks	36.0 wks	2 days old	Death after 2 days of ventilation due to respiratory failure (pulmonary hypoplasia; prematurity, hydrops)
57	very large	yes	No surgery (due to maternal social ci)	31.3 wks	5 hours old	Death after 5 hours of ventilation due to respiratory failure (autopsy: pulmonary hypoplasia, L pneumothorax; prematurity, hydrops)
56	very large	yes	No surgery (due to maternal uterus didelphus ci)	25.3 wks	½ hour old	Death after ½ hour of ventilation due to respiratory distress syndrome, pulmonary hypoplasia, bilat. pneumothorax, pneumoretroperitoneum; prematurity, hydrops, (questionable renal agenesis)
58	very large	yes	TOP	23.0 wks	23.0 wks	TOP due to preterm labor (autopsy: prematurity, hydrops, thoracic and abdominal organ compression)
60	very large	yes	TOP	25.0 wks	25.0 wks	TOP due to maternal mirror syndrome (prematurity, hydrops)
59	very large	yes	TOP	22.4 wks	22.4 wks	TOP due to social indication (autopsy: prematurity, hydrops, bilat. olivary nuclei dysplasia of unclear clinical significance, bilat. kidney hemorrhage)
42	large	no	TOP	24.7 wks	24.7 wks	TOP probably due to maternal medical indications (the mother died 5 years after this pregnancy) (prematurity, NO hydrops)

(wks = gestational weeks, S/P = Status post, ci = contraindication, TOP = termination of pregnancy)

The major cause of death as shown in Table 1 was termination of pregnancies and delayed or non-attempted fetal surgery of hydropic fetuses (Figure 2 and 4.2).

Ultimately, there were only 3 children who did not survive in the invasive fetal treatment group of 14 children (21%, 3 of 14). All other children of the fetal non-intervention groups did survive (100%, 40 of 40 patients).

5.2.2 The early respiratory outcome correlated with the children's age at surgical intervention

The early respiratory outcome in the first 2 months of the children's lives was categorized according to the respiratory symptoms and the need of respiratory support as described in the PATIENTS AND METHODS section. The differences in the early respiratory outcomes of the survivors depended significantly ($p<0.001$) on the age at surgical intervention (5 intervention groups, as classified in the PATIENTS AND METHODS section). Of the 11 neonates surviving invasive fetal treatment, 10 (91%) had severe early respiratory symptoms. Of the 12 children requiring neonatal surgery, 6 had severe and 3 had moderate early respiratory symptoms, and only 3 neonates were electively operated. Of the surviving children in the childhood surgery group (15 cases) and in the no-surgery group (13 cases), all but one were respiratory-wise asymptomatic (17 cases) or only mildly symptomatic (10 cases) early after birth (Table 3). As expected, more aggressively treated children had more severe early respiratory symptoms and they required longer days on mechanical ventilation, in the intensive care unit (ICU), or both ($p<0.001$) (Table 2.1).

Table 2.1.
Strong relationship between early outcome and surgical treatment group (N=51 survivors)

Early outcome (of 51 survivors)	**Fetal surgery** (11 cases, incl. 4 shunts/ aspirations)	**Neonatal surgery** (12 cases)	**Childhood surgery** (15 cases, incl. 4 in late childhood)	**No surgery** (13 cases)
<33 wks GA @ birth	5	/	/	/
33-37 wks GA @ birth	4	4	3	3
>37 wks GA @ birth	2	8	12	10
No respiratory symptoms	1	1	8	9
Mild respiratory symptoms	/	2	6	4
Moderate respiratory symptoms	/	3	1	/
Severe respiratory symptoms	10	6	/	/
Ventilatory support (mean days)	19.7	5.7	/	/
ICU (mean days)	42.1	11.3	1.2	3.4
Hospitalization (mean days)	45.6	11.8	2.7	4.5
Initial non-respiratory difficulties	8	5	2	3
Prolonged non-respiratory difficulties	6	6	2	5

5.2.3 Prematurity was a significant factor of the early outcome, and it predominated the (potential) fetal intervention group

The gestational age at delivery was significantly associated (p=0.001) with the affiliation to a surgical intervention group (4 TOPs excluded). Six of the eight severely premature babies born alive (<33 weeks' gestation) were in the invasive fetal treatment group (one died 2 days after birth); the other two severely premature neonates were potential fetal treatment patients, who died within hours after birth due to maternal contraindications for fetal interventions. The 51 survivors were born between 25.9 to 41.4 weeks' gestation. Only 2 (18%) of the 11 babies surviving after invasive fetal treatment were born after 38 weeks' gestation (term), whereas 75% (30 of 40 cases) of the surviving babies in the fetal non-intervention groups were born at term, as shown in Table 2.1.

Preterm labor (PTL) and premature rupture of membranes (PROM) were the two reasons for premature delivery in the fetal intervention group. Following fetal intervention, 85% (11/13) of the patients were born prior to 36.3 weeks' gestation due to PTL (9%, 1/11), PROM (9%, 1/11), or mostly due to both (55%, 6/11); (data were not available for 2 cases, case no. 41 and case no. 48).

The early respiratory outcomes as well as the interim respiratory childhood outcomes significantly correlated with the gestational age at delivery ($p<0.001$). Thus, the need for mechanical ventilation and ICU treatment was significantly higher for children who were prematurely born ($p=0.006$). However, the respiratory outcomes improved remarkably with long-term observation, as described in the following CHAPTER 5.2.4.

Initial transient non-respiratory difficulties of the survivors, such as hyperbilirubinemia, anemia, arterial hypo- or hypertonia, electrolyte irregularities, or sepsis, were also significantly associated with prematurity ($p=0.005$). Of the 19 survivors born at less than 38 weeks' gestation, 12 had perinatal non-respiratory symptoms (Table 2.1). However, these problems resolved in the neonatal period. More resistant to treatment were prolonged difficulties with feeding, weight gain, and GERD, which also tended to be associated with prematurity ($p=0.08$). Of the 19 survivors born less than 38 weeks' gestation, 10 had such difficulties (Table 2.1). The prolonged non-respiratory difficulties were still present at the last follow-up in half of the symptomatic cases (5 of 10 cases), yet, they all had improved to a milder stage, mostly by the age of 2 years old (see CHAPTER 5.2.7). Prematurity was a significant determining factor for the early respiratory and non-respiratory outcomes, but the early symptoms mostly resolved in the course of the follow-ups.

5.2.4 The final respiratory outcome was excellent, and it was not determined by the early respiratory outcome

The significant differences of the children's respiratory outcomes in the early postnatal phase ($p=0.001$) faded at large with long-term observation ($p>0.94$). Normally the children grew out of their initial respiratory difficulties soon after birth or during infancy. In the neonatal period, 13 (41%) of the 32 surviving children recovered with symptoms after birth (including 5 severely symptomatic neonates, of whom 4 were treated during fetal life). Thirty-four percent (11 of 32 cases) improved until the age of 2 years old, and 16% (5 of 32 cases) got better between 2 and 4 years old. Only 3 (9%) patients did not improve to the full extent so far, as described below and in Tables 2.2 and 3.

At the children's last follow-up (mean: 5.9 ± 3.3 years, range: 1.3 to 13.1 years of age), a total of 94% were asymptomatic or had only mild symptoms (38 of 51 survivors, 74%, were asymptomatic and 10 of 51 survivors, 20% had only mild symptoms). Four children exhibited minor labored breathing on exertion and the other 6 of the 10 mildly symptomatic children exhibited mild asthmatic symptoms. Only three patients after surgery (one of each distinct surgical treatment group) had at their last follow-up at 3, 5, and 12 years old moderate respiratory symptoms such as manifest asthma, frequent pulmonary infections, and limited physical endurance (Table 3). This was one of the important findings of the study: the children's final respiratory outcome was excellent, and it was independent of the children's early respiratory outcomes or the affiliation with a distinct surgical treatment group (Table 2.2).

Table 2.2.
No relationship between long-term respiratory outcomes and surgical treatment group

Long-term respiratory outcome	**Total patients** (60 cases)	**No surgery** (15 cases)	**Childhood surgery** (15 cases, incl. 4 in late childhood)	**Neonatal surgery** (12 cases)	**Fetal surgery** (14 cases, incl. 4 shunts/ aspirations)	**TOP** (4 cases)
No symptoms	38	11	11	8	8	/
Mild symptoms	10	2	3	3	2	/
Moderate symptoms	3	/	1	1	1	/
Severe symptoms	/	/	/	/	/	/
Alive	**51**	**13**	**15**	**12**	**11**	**/**
Dead	**9**	**2**	**/**	**/**	**3**	**4**

5.2.5 Interim respiratory outcomes correlated with early respiratory outcomes during the period before significant improvement

Interim respiratory symptom severity, observed within the period before significant improvements, correlated with the level of early respiratory symptoms ($p<0.001$). However, the age when significant improvement was achieved did not correlate with the severity of the early symptoms ($p>0.6$).

Only 2 (6%) of the 31 surviving children who were asymptomatic or mildly symptomatic early after birth developed a moderately worsened respiratory condition during childhood. In the group of the 20 surviving children with severe or moderate early respiratory symptoms, 13 (65%) had prolonged severe (7 of 13 cases) or moderate (6 of 13 cases) interim respiratory symptoms prior to the age of 2 years (8 of 13 cases), 4 years (3 of 13 cases), or until the last follow-up (2 of 13 cases). The remaining 7 children (7 of 20 cases) in this group had already improved in the neonatal period (6 of 7 cases) or in the first year (1 of 7 case), and all 7 children were asymptomatic or mildly symptomatic thereafter (Table 3).

The children with severe interim respiratory symptoms required re-hospitalizations in childhood (4 cases after fetal surgery, 1 case after neonatal surgery, 1 case for delayed symptomatic surgery) or extended oxygen treatment during infancy (1 case after neonatal surgery), as described in the following CHAPTER 5.2.6. Despite the above-described interim respiratory symptoms, final respiratory outcomes were excellent and not determined by the interim respiratory outcomes, as it was not determined by the early respiratory outcomes.

5.2.6 Re-hospitalizations in childhood were required for 55% of the children after invasive fetal treatment and for 54% of the non-operated children for delayed surgery

Of the 28 children who were not operated on until the age of one month, 15 (54%) were re-hospitalized after the perinatal period, either for symptomatic delayed surgery (6 cases, 2.4 months to 4.3 years old) or for primary elective surgery (9 cases, 5 months to 4.5 years old). Four of the six children who were operated on for delayed symptoms had prolonged hospital stays (9 days to 34 days) due to postoperative complications. One non-operated child (case no. 12) was re-hospitalized not for surgery, but due to pneumonia that he developed at the age of 2 years. Among the 12 children operated on neonatally, only 2 were re-hospitalized due to recurrent respiratory infections (one at 6 months old and the other at 3 ½ years old).

Re- hospitalization(s) were required for 6 (55%) of the 11 invasive fetal treatment survivors, because of severe (4 cases) or mild (2 cases) interim respiratory symptoms. Three of these patients were re-hospitalized during infancy for 3 to 15 days due to

pneumonia, respiratory syncytial virus bronchiolitis, or both. One child on whom multiple cyst aspirations had been performed before birth required postnatal surgery on a bronchogenic cyst at 6 months due to mild respiratory symptoms (case no. 41). Another fetal surgery patient (case no. 55) required 16 days of re-hospitalizations during infancy. She was finally re-operated on at the age of 3 ½ years for symptomatic CCAM residual and thoracic scar deformation. This case is discussed in detail in PART II of this doctoral thesis. The patient with the longest re-hospitalization interval of 153 days (case no. 54) required an implantation of a tissue expander at 2 months old and aortopexy at 3 ½ months old due to severe mediastinal shift after fetal pneumonectomy.

All children recovered well from the symptoms and re-hospitalizations (Tables 2.2 and 3). Only three children had moderate respiratory symptoms at their last follow-ups. An important conclusion could be drawn: The final outcomes of the children were excellent, despite re-hospitalizations due to interim respiratory problems.

5.2.7 Other non-respiratory complications were postoperative complications, prematurity-associated feeding problems, transient cardiac symptoms, and rare congenital anomalies

Postoperative late complications, such as a pectus excavatum and a prominent thoracic scar, developed six times and five times, respectively, in 8 (21%) of the 38 survivors who had received operations. Remarkably, all 8 children were operated on prior to the age of 1 month (including 3 fetal surgery cases). None of these children required surgical revision by the age of 3 to 12 years old, except for one re-operated child (case

no. 55), as described above in CHAPTER 5.2.6 and discussed in detail in PART II of this doctoral thesis.

Prolonged problems with feeding, weight gain, and GERD occurred close to twice as much in prematurely born survivors (10 of 19 cases born <37 weeks' gestation, 53%) than in term born survivors (9 of 32 cases born >37 weeks' gestation, 28%), with a trend to statistical significance (p=0.08). However, these difficulties had mostly diminished to a milder stage by the age of 2 years. The fact that 8 (16%) of 51 surviving children had low body weight (<3rd percentile) at their last follow-ups was not linked to any initial feeding problems (p>0.13) or prematurity (p>0.3). It was also independent of the prior surgical treatment strategy (p>0.3) and of the early and final respiratory outcomes (p>0.5).

There were 10 children of the 51 survivors who presented with transient functional cardiac symptoms such as arrhythmia (3 cases), cardiac enlargement (4 cases), and heart murmurs (7 cases, combinations included). These symptoms disappeared in the neonatal period or at the latest at 6 months of age. None of these children had a congenital, anatomic heart disease. No association between the cardiac symptoms and prematurity (p>0.1), early respiratory outcomes (p>0.1), or surgery group affiliation (p>0.3) could be assessed. Also, the extension of a prenatal mediastinal shift had no influence on the cardiac symptoms (p>0.1).

Other major congenital anomalies were found in 5 (8.3%) of the 60 study cases. A prenatal ultrasonographic diagnosis of these anomalies was possible for only 2 (3.3%, 2 of 60) of these cases. One fetal surgery case developed Asperger syndrome, a milder variant of autism. One child in the neonatal surgery group was found to have Mayer-Rokitansky-Küster-Hauser syndrome (with right renal agenesis and vaginal atresia), and

another child in this group had albinism. One child required craniofacial surgery for congenital craniosynostosis shortly after the CCAM operation in late infancy. At their last follow-ups, all of these 4 children had been enrolled in the regular (pre-) school system and were doing fine. The fifth case, a terminated fetus (case no. 59), was found through autopsy to have bilateral dysplasia of the olivary nuclei of unclear clinical significance. There was no obvious link between the congenital anomalies and a distinct intervention group or prematurity. However, the number of cases was too small to carry out statistically significant calculations regarding the incidence of these anomalies.

Table 3.
Early and long-term respiratory outcomes of 60 patients with prenatally diagnosed cystic lung lesions

Case no.	Prenatal mass size (final)	Hydrops	Prenatal diagnosis	Age @ birth (fetal wks)	Age @ surgery (postnatal DOL and/or fetal wks)	Age @ improvement (last incidence of respiratory symptoms)	Age @ last f/u (years)	Early respiratory outcome (symptoms)	Long-term respiratory outcome (symptoms)
1	**vanished**	no	BPS (solid)	39.4	no	0	10.5	**no**	**no**
2	**vanished**	no	CCAM (solid)	40.4	no	0	7.1	**no**	**no**
3	**vanished**	no	CCAM (solid)	39.3	no	0	3.0	**no**	**no**
4	**vanished**	no	CCAM (solid)	39.6	no	0	1.7	**no**	**no**
5	**vanished**	no	Hybrid (solid)	39.0	DOL1617	0	5.1	**no**	**no**
6	**vanished**	no	Hybrid (microcystic)	36.1	DOL 995	0	3.4	**no**	**mild**
7	**vanished**	no	CCAM (macrocystic)	39.6	DOL 630	(2 incidences @ 10 mo + 1.5 yo)	8.3	**no**	**no**
8	**small**	no	BPS (solid)	37.4	no	0	3.5	**no**	**no**
9	**small**	no	CCAM (microcystic)	41.4	no	0	3.3	**no**	**no**
10	**small**	no	CCAM (solid)	38.4	no	(incidences @ 4 mo - 2 yo)	2.0	**no**	**mild**
11	**small**	no	BPS (solid)	33.3	no	neonatal (incidences @ 3 yo - 6 yo)	8.4	**mild**	**no**
12	**small**	no	CCAM (microcystic)	36.1	no	neonatal (1 incidence @ 2 yo)	8.8	**mild**	**no**
13	**small**	no	CCAM (n/a)	38.0	no	neonatal + episode @ 1 yo - 3 yo	9.3	**mild**	**mild**
14	**small**	no	CCAM (solid)	36.4	DOL1581	neonatal (1 incidence periop @ 3 yo - 4 yo)	10.0	**mild**	**no**
15	**small**	no	CCAM (microcystic)	40.7	DOL 350	0	3.7	**no**	**no**
16	**small**	no	CCAM (microcystic)	40.6	DOL 188	neonatal **+** episode @ 2 yo - 4 yo	4.3	**mild**	**mild**
17	**small**	no	CCAM (microcystic)	39.0	DOL 153	neonatal	2.1	**mild**	**no**
18	**small**	no	CCAM (microcystic)	39.7	DOL 152	0	3.2	**no**	**no**
19	**small**	no	CCAM (solid)	38.9	DOL 147	0	3.9	**no**	**no**
20	**small**	no	BPS (solid)	38.9	DOL 1	0	6.1	**no**	**no**
21	**moderate**	no	CCAM (macrocystic)	40.0	no	0	7.7	**no**	**no**
22	**moderate**	no	CCAM (solid)	40.7	no	0	1.3	**no**	**no**
23	**moderate**	no	CCAM (n/a)	41.4	no	neonatal	2.7	**mild**	**no**
24	**moderate**	no	Hybrid (microcystic)	38.0	DOL 317	(2 incidence @ periop 10mo+ 2yo)	7.9	**no**	**no**
25	**moderate**	no	CCAM (solid)	38.7	DOL 283	neonatal **+** episode from 5 mo until f/u @ 5 yo	5.2	**mild**	**moderate**
26	**moderate**	no	CCAM (microcystic)	36.9	DOL 184	6 mo (1 incidence @ 1.5 yo)	3.4	**moderate**	**no**
27	**moderate**	no	CCAM (n/a)	39.0	DOL 180	episode @ 6 mo - 2.5 yo	2.5	**no**	**mild**
28	**moderate**	no	CCAM (n/a)	40.0	DOL 71	2.5 mo	12.7	**mild**	**no**
29	**moderate**	no	Hybrid (n/a)	40.0	DOL 31	neonatal (incidences @ 2 yo - 5 yo)	13.1	**moderate**	**mild**

30	**moderate**	no	CCAM (microcystic)	38.1	DOL 10	3 mo (1 incidence @ 2 yo)	4.2	**moderate**	**no**
31	**moderate**	no	CCAM (microcystic)	33.1	DOL 6	episode until f/u @ 3 yo	3.0	**severe**	**moderate**
32	**moderate**	no	CCAM (macrocystic)	34.0	DOL 5	neonatal **+** episode @ 2 yo - 3.5 yo	5.3	**moderate**	**no**
33	**moderate**	no	CCAM (microcystic)	39.6	DOL 1	neonatal **+** episode @ 2 yo - 4 yo	6.5	**severe**	**no**
34	**moderate**	n/a	CCAM (n/a)	40.0	DOL 151	5 mo	5.9	**mild**	**no**
35	**large**	no	CCAM (microcystic)	38.3	DOL 3	neonatal	10.4	**mild**	**no**
36	**large**	no	CCAM (macrocystic)	35.9	DOL 3	neonatal	5.6	**severe**	**mild**
37	**large**	no	CCAM (microcystic)	38.3	DOL 2	neonatal (1 incidence @ 4 mo)	4.2	**mild**	**no**
38	**large**	no	CCAM (microcystic)	40.7	DOL 2	neonatal **+** episode @ first years	8.8	**severe**	**no**
39	**large**	no	CCAM (solid)	38.0	34 wks & DOL 6	1.2 yo	2.6	**severe**	**mild**
40	**large**	no	BPS (solid)	35.6	26 wks & 26.6 wks & DOL 4	neonatal (1 incidence @ 3 mo - 5 mo)	6.1	**severe**	**no**
41	**large**	no	CCAM (macrocystic)	36.3	24 wks & 25 wks & 26 wks & DOL 198	(1 incidence periop @ 6 mo)	8.1	**no**	**no**
42	**large**	no	CCAM (n/a)	24.7	no	/	/	**TOP**	**death**
43	**very large**	no	CCAM (solid)	38.4	DOL 3	2 yo	3.6	**severe**	**no**
44	**very large**	no	CCAM (solid)	35.7	DOL 1	1.5 yo	6.6	**severe**	**mild**
45	**very large**	no	CCAM (n/a)	32.7	25.6 wks	3.5 yo **+** episode from 8 yo until f/u @ 12 yo	12.8	**severe**	**moderate**
46	**very large**	no	CCAM (n/a)	30.4	24.4 wks	1 yo	8.9	**severe**	**no**
47	**very large**	no	CCAM (macrocystic)	40.6	23.1wks & 27.7 wks & DOL 1 & DOL 6	neonatal	9.2	**severe**	**no**
48	**very large**	yes	CCAM (microcystic)	36.0	29.7 wks	/	/	**death**	**death**
49	**very large**	yes	CCAM (macrocystic)	34.0	29 wks	/	/	**severe**	**death** (2.5 mo)
50	**very large**	yes	CCAM (microcystic)	29.0	28 wks	/	/	**death**	**death**
51	**very large**	yes	CCAM (macrocystic)	34.1	27.7 wks	neonatal (incidences @ 1 yo - 1.3 yo)	2.2	**severe**	**no**
52	**very large**	yes	CCAM (macrocystic)	33.3	25.9 wks	neonatal	2.3	**severe**	**no**
53	**very large**	yes	CCAM (macrocystic)	25.9	24.1 wks	2 yo	12.9	**severe**	**no**
54	**very large**	yes	CCAM (solid)	32.9	22.7 wks	2 yo	3.2	**severe**	**no**
55	**very large**	yes	CCAM (macrocystic)	29.7	20.4 wks & DOL 1282	1.5 yo	4.3	**severe**	**mild**
56	**very large**	yes	CCAM (solid)	25.3	no	/	/	**death**	**death**
57	**very large**	yes	CCAM (n/a)	31.3	no	/	/	**death**	**death**
58	**very large**	yes	CCAM (solid)	23.0	no	/	/	**TOP**	**death**
59	**very large**	yes	CCAM (macrocystic)	22.4	no	/	/	**TOP**	**death**
60	**very large**	yes	CCAM (solid)	25.0	no	/	/	**TOP**	**death**

(DOL= day of life, yo = year(s) old, mo = month(s) old, wks = gestational weeks, n/a = not available)

5.3 The prognostic value of the prenatal ultrasound parameters

5.3.1 Not the distinct prenatal diagnosis, but the type of the cystic lung lesion was a potential predictive factor of the early outcome

The prenatal ultrasonographic diagnoses of the 60 study cases were CCAM (51 cases), BPS (5 cases), and a CCAM-BPS-hybrid (4 cases). A histopathologic diagnosis was established in 40 of the 60 study cases. For the other 20 cases, a histopathologic diagnosis was not available, either because no surgery was done (13 cases) or the reports of the surgery (3 cases) or of the autopsy (4 cases) were not accessible to me. The prenatal diagnosis was confirmed in 29 of the 40 cases, which means an agreement between the prenatal ultrasonographic diagnosis and the histopathologic diagnosis was achieved in 72.5% of the cases. Nine of the prenatally diagnosed CCAM cases were misdiagnosed and turned out to be BPSs (4 cases), CCAM-BPS-hybrids (3 cases), a bronchogenic cyst (1 case), and a bronchiectasis (1 case) at pathology. Two prenatally misdiagnosed CCAM-BPS-hybrid cases were identified as BPSs at pathology.

Prenatal color Doppler sonography was applied in 40 of the 60 study cases and it provided information about a potential systemic feeding vessel from the aorta to the mass. Color Doppler sonography, applied in addition to the conventional prenatal ultrasonography, has an influence on the prenatal diagnosis. A histopathologic diagnosis was established in 25 of these 40 cases. The ultrasonographic diagnosis supported by Color Doppler imaging agreed with the pathological findings in 80% of the cases (20 of 25 cases). In contrast, a prenatal ultrasonographic diagnosis without color Doppler imaging was correct in only 60% (only 9 of 15 study cases with a conventional prenatal ultrasonographic diagnosis and a histopathologic diagnosis had a prenatal correct

diagnosis). Color Doppler imaging increased the positive predictive value for correct prenatal distinct diagnosis.

The type of the cystic lung lesion was characterized using the Stocker type classification in 50 of the 60 study cases, as described in the PATIENTS AND METHODS section. There were 12 macrocystic type I cases, 17 microcystic type II cases, and 21 solid appearing type III cases (Table 3). The Stocker type classification matched roughly with the plain categories of sonographic appearance introduced in this study, since the sonographic appearance of 56 of the 60 study cases was characterized as predominantly cystic in 9 cases, mixed in 25 cases, and predominantly solid in 22 cases. Of the 56 cases characterized into solid, cystic, or mixed, 37 had a histopathologic diagnosis. Comparing the sonographic appearances of the lung lesions with the histopathologic diagnoses, it again becomes clear that the distinct prenatal diagnosis, solely based on the sonographic appearance of the lesion, is not very specific. Of the 10 fetal lung lesions with the sonographic appearance of a solid tumor, 6 (60%) were CCAMs, 3 (30%) were BPSs, and 1 (10%) was a bronchiectasis at pathology. The 27 fetal lung lesions with the sonographic appearance of a cystic or mixed tumor showed a comparable pattern of histopathologic diagnoses with 21 (78%) CCAMs, 3 (11%) BPSs, 2 (7%) CCAM-BPS-hybrids, and 1 (4%) bronchogenic cyst. This breakdown, from the lesions' sonographic appearances into their histopathologic distinct diagnoses, demonstrates that using conventional prenatal ultrasound without color Doppler imaging does not establish a distinct correct prenatal diagnosis. Consequently, I did not include the distinct prenatal ultrasonographic diagnosis due to its inaccuracy into my statistical analyses of prenatal outcome predictors. Instead, I tested the postoperative or post-

autopsy, histopathologic diagnosis for its prognostic value and still there was no significant difference in the data set between CCAM and BPS concerning the early outcome ($p>0.2$).

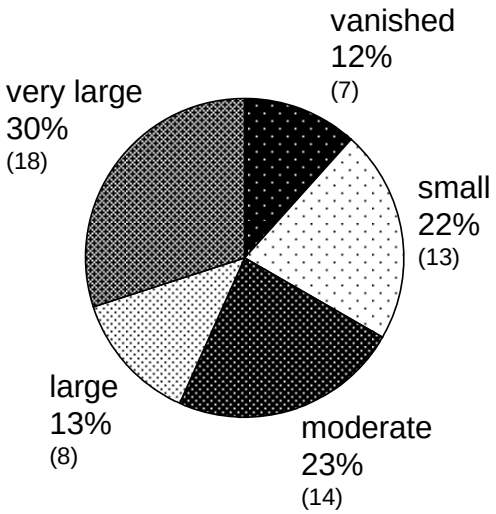
However, the plain description of the lesions' sonographic appearance and the Stocker-types were of some prognostic value concerning the early outcome. The predominantly solid appearing lung lesions (Stocker type III) in my study showed a tendency ($p=0.01$ to $p=0.07$) to be of smaller final mass sizes and better early respiratory outcomes than mixed lung lesions or large-cystic, Stocker type I lesions. Masses with large Stocker type I cysts increased significantly more often during pregnancy and about 2 gestational weeks earlier ($p<0.023$) than solid, Stocker type III lesions or small-cystic, Stocker type II lesions which in contrast regressed more often (Table 4). In one case (no. 59), the macrocystic Stocker type I lesion grew rapidly from a small sized lesion to a very large mass before the pregnancy was terminated (Table 1). The significant factor concerning the early outcome was the size of the cysts, not the predominance of the cystic component in the mass. The larger the cysts grew, the larger the final size of the mass became ($p<0.023$) and the more severe the early respiratory symptoms became ($p<0.028$). Moderate or severe early respiratory symptoms were present in 70% (7 of 10 cases; 2 deaths excluded) of the surviving newborns with large Stocker type I cysts, whereas 70% (23 of 33 cases; 5 deaths excluded) of the survivors with solid Stocker type III lesions or small-cystic Stocker type II lesions were asymptomatic or only mildly affected after birth. However, all of these children had a favorable final respiratory outcome, independent of the type of the cystic lung lesion.

5.3.2 The final size of the mass was the most important predictor of the early outcome

Using prenatal ultrasound, the cystic lung lesions of the 60 fetal patients were initially diagnosed between 9.9 and 34.9 weeks' gestation (mean 20.7 ± 3.8 weeks' gestation) after the LMP. Serial ultrasound reports or scans were available for 52 (87%) of the 60 fetuses; and in 49 of these 52 cases, more than three ultrasound reports or scans existed. Using the serial ultrasound reports or scans of these 52 cases, it was possible to determine the progression or regression of the size of the masses and of other prenatal symptoms.

The cystic lung lesions of the 60 fetuses were initially very large in 11 fetuses, large in 18 fetuses, moderate in 18 fetuses, and 11 fetuses had small lesions at initial diagnosis. For one moderate sized lesion (no. 34) and one prenatal shunt case (no. 39) the initial data were missing. At the end of the prenatal observational period or until fetal intervention, most mass sizes had changed, and the final sizes of the 60 lesions became very large (18 cases), large (8 cases), moderate (14 cases), and small (13 cases). In 7 cases the masses disappeared (Figure 5; Tables 3 and 4).

Figure 5. Prenatal final size of the lung lesions (N=60)



Details about the changes of the mass sizes were derived from the 52 serially scanned lesions: 41 of the 52 mass sizes changed and 11 of the 52 masses did not change at all, relative to the size of the fetus. Thirteen of the 52 masses increased; 16 of the 52 masses increased and subsequently decreased, either back to the original size (7 cases) or to a smaller size (9 cases, including 2 vanished masses); and 12 of the 52 masses primarily regressed (including 4 vanished masses). In summary, 25% (13 of 52 serially scanned masses) increased, 35% (18 of 52 masses) had the same relative size at the end of the observational period, as they had at initial diagnosis; and 40% (21 of 52 masses) regressed.

Tracking the growth of the masses from their initial size to the final size, I noticed that each size category had a different growth pattern. Most of the initially very large masses stayed very large (10 of 11 cases, 91%); the as large categorized masses regressed in 56% (10 of 18 cases) and increased in 33% (6 of 18 cases); the moderate masses almost equally grew larger (7 of 18 cases, 39%), or smaller (6 of 18 cases, 33%), or stayed the same size (5 of 18 cases, 28%); and the initially small masses were mostly small or vanished (8 of 11 cases, 73%) at the end of the prenatal observational period.

Another interesting finding concerned the timing of the mass size changes. Masses that had become large or very large at any point in time during fetal life (independent of the final size of the mass) were more likely ($p=0.06$) to be diagnosed at an earlier gestational age and – as the case may be – to increase and (subsequently) regress earlier than small or moderate sized masses. The large and very large masses at maximum size were diagnosed at a mean of 20.1 ± 3.3 weeks' gestation (9.9 to 28.0 weeks' gestation) and did – as the case may be – increase at a mean of 22.3 ± 1.5 weeks' gestation (19.9 to 26.3 weeks' gestation) and regress at a mean of 27.6 ± 3.7 weeks' gestation (23.4 to 34.0 weeks' gestation). In comparison, the masses with a small or moderate maximum size were later diagnosed at a mean of 22.3 ± 4.7 weeks' gestation (13.0 to 34.9 weeks' gestation) and – as the case may be – also increased later at a mean of 23.8 ± 2.1 weeks' gestation (21.7 to 26.7 weeks' gestation) and regressed later at a mean of 30.5 ± 3.8 weeks' gestation (22.9 to 37.0 weeks' gestation).

The size of the lesion was the most crucial factor in the early outcomes of the fetuses. The final and the maximal prenatal sizes of the masses were significantly associated ($p<0.001$ to $p<0.003$) with mortality, the need for pre- or postnatal surgical

treatment, and along with the early respiratory difficulties, with the requirement of ventilatory support and intensive care treatment. Mortality almost exclusively occurred in fetuses with ultimately very large masses (8 of 9 deaths, including 3 TOPs) (Table 1 and Figure 2). The survivors of ultimately very large lesions (10 of 18 cases) all had severe early respiratory symptoms and required mechanical ventilation for more than 3 days (including 4 children with more than 15 days of ventilation). All surviving 17 children with ultimately large or very large lesions (26 cases minus 9 non-survivors) were operated on in the fetal (11 of 17 cases, 65%) or neonatal (6 of 17 cases, 35%) period. None of the children with ultimately small or vanished lesions (20 cases) died or had more than mild respiratory symptoms early after birth. Most of them were asymptomatic (14 of 20 cases, 70%). None of them needed ventilatory support except for one child who was ventilated only as a precaution, following neonatal surgery. Most of the children with small or moderate sized lesions at the end of the pregnancy (34 cases) did not require surgical treatment or were operated on later in childhood (28 of 34 cases, 82%) (Tables 3 and 4). Prematurity and prematurity-associated transient non-respiratory difficulties were mostly a problem of children with expansive masses. The gestational age at birth and the absolute birth weight were significantly lower ($p<0.001$ to $p<0.002$) in the very large mass size group (mean: 32.6 ± 4.2 weeks' gestation, 2172 ± 765 gram; TOPs excluded), compared to the small mass size group (mean: 38.6 ± 1.9 weeks' gestation, 3346 ± 662 gram).

In contrast to the high prognostic value of the final or maximal size of the mass, the initial mass size, if it was moderate or large, did not predict the early outcome. If the initial mass size was at one of the extreme ends (very small or very large), it would more

likely keep its size during pregnancy (for information about the specific prenatal growth patterns of the different mass sizes, please refer to the fourth paragraph of this CHAPTER 5.3.2), and herewith it predicted ($p<0.002$ to $p<0.018$) in these cases the early outcome as much as the final size did.

The differentiation into early respiratory outcome and long-term respiratory outcome turned out to be essential, since the long-term outcome was not predictable ($p>0.6$) by the prenatal size of the mass, in contrast to the early outcome. The final outcomes of the children were excellent. More than 70% of the surviving children of any prenatal mass size category were asymptomatic at final follow-up and no child had severe symptoms. Only three children with prenatally different ultimate mass sizes (one very large mass and two moderate masses) and different surgical treatment strategies (one fetal surgery, one neonatal surgery, and one childhood surgery) had moderate symptoms at the end of the study, as described in CHAPTER 5.2.4 and in Tables 3 and 4.

Table 4.
Association between the prenatal final mass size, other prenatal symptoms, and respiratory outcomes

Other prenatal symptoms		**Very large masses** (18 cases)	**Large masses** (8 cases)	**Moderate masses** (14 cases)	**Small + vanished masses** (13+7 cases)
Type of lesion	Stocker type I	7 ***	2 *	2 *****	1 *
	Stocker types II and III	8	5	7	18
Hydrops		13	/	/ *	/
Mass- or hydrops-associated symptoms	Med. shift (marked & mod.)	18	3 *	4 *	3
	Med. shift (NO & mild)	0	4	9	17
	Skin edema	11	0	0 *	0
	Ascites	15	0	0 *	1
	Pleural effusion	6	3	0 *	0
	Pericardial effusion	4	0	2 *	4
	Poly	11	4 **	4 *	3
	Placentomegaly	12	1 **	0 *	1
Surgical intervention group	TOP ♣	5	1	0	0
	Fetal surgery	11	3	0	0
	Neonatal surgery	2	4	5	1
	Late childhood surgery	0	0	6	9
	No surgery	0	0	3	10
Outcome (60 cases)	**Dead** (9)	**8**	**1**	***/***	***/***
	Alive (51)	**10**	**7**	**14**	**20**
Early respiratory outcome of the survivors (51 cases)	No symptoms	0	1	4	14
	Mild symptoms	0	2	4	6
	Moderate symptoms	0	0	4	0
	Severe symptoms	10	4	2	0
Long-term respiratory outcome of the survivors (51 cases)	No symptoms	7	5	10	16
	Mild symptoms	2	2	2	4
	Moderate symptoms	1	0	2	0
	Severe symptoms	0	0	0	0

♣ here included 2 potential fetal treatment cases, not performed due to maternal contraindications,
* 1 case data not available, ** 2 case data not available, *** 3 case data not available, ***** 5 case data not available

5.3.3 A hydrops fetalis and some of the hydrops-associated symptoms were associated with the size of the mass and they were very strong predictors of the early outcome

A hydrops developed in 13 (22%) of the 59 fetuses (there was a lack of data from case no. 34 with a moderate sized lesion). According to Evans [51], a hydrops fetalis is classically defined as an abnormally increased fluid accumulation in two or more serous cavities and/or skin edema. In addition, a modified definition of a hydrops was applied to two of the study cases (no. 54 and 58) which had marked ascites combined with placentomegaly and polyhydramnios. A hydrops developed at a mean gestational age of 23.0 ± 3.2 weeks' gestation (18.4 to 28.4 weeks' gestation), which was about 1 week after the mean gestational age of mass size increase of very large masses (as described in CHAPTER 5.3.2). In most cases the hydrops rapidly worsened until fetal surgery or termination (8 of 13 hydrops cases), or it was already advanced at the time of detection (3 of 13 hydrops cases). A regression of a hydrops was observed between 1 to 3 weeks after fetal tumor resection in all 5 hydropic fetal surgery survivors.

Skin edemas were present in 11 (85%) of the 13 hydropic fetuses and in 9 of them it was marked (Figure 2). All 13 (100%) hydropic fetuses developed ascites and it was marked in all but one of them. Only 3 (7%) of 46 non-hydropic fetuses (lack of data from case no. 34) had mild ascites. As a sign of substantial fluid accumulation the "growth" of hydropic fetuses was significantly larger than their dates ($p<0.01$). Too-large-for-dates (fetal size > 90^{th} percentile) were 6 (46%) of 13 hydropic fetuses with skin edema, ascites, or both. Pleural effusions were observed in 6 (46%) of 13 hydropic cases, all of them were combined with skin edema (6 of 6 cases), and 2 of them were marked (2 of 6 cases, including 1 BPS). Only 7% (3 of 46 cases; there was a lack of data from case no.

34) of the fetuses without frank hydrops developed pleural effusion. Skin edema, ascites, and pleural effusion were significantly related to a hydrops ($p<0.001$, $p<0.001$, and $p=0.004$, respectively). In contrast, pericardial effusion was not significantly associated with a hydrops ($p>0.2$) and it was recorded in nearly the same percentage of hydropic cases (15%, 2 of 13 hydrops cases) as non-hydropic cases (17%, 8 of 46 non-hydropic cases, there was a lack of data from case no. 34) (Table 4).

Placentomegaly and polyhydramnios were the two prenatal symptoms that were not included in the classic definition of a hydrops fetalis [51] but they were also significantly related to a fetal hydrops ($p<0.001$ and $p=0.005$, respectively). Of 13 fetuses with a hydrops, 12 (92%) had placental enlargement (5 marked, 6 moderate, and 1 mild) and 9 (69%) had polyhydramnios (3 marked, 2 moderate, and 4 mild). Placental enlargement and polyhydramnios occurred in only 2 (4%) and 13 (24%) of 54 non-hydropic cases, respectively (Table 4; data not available in three cases: TOP case no. 42, fetal shunt case no. 39, and moderate sized lesion case no. 34).

The development of a hydrops was significantly associated with the final size of the mass ($p<0.001$). All 13 hydropic fetuses had very large masses or in other words, 72% (13 of 18 cases) of the fetuses with ultimately very large lesions developed a hydrops (Figure 2, Tables 3 and 4). I could also demonstrate that the classic hydrops-associated symptoms of ascites, skin edema, and pleural effusion as well as the non-classic hydrops-associated signs of placentomegaly and polyhydramnios were, if separately calculated, also significantly associated with the final mass size ($p<0.001$ to $p<0.008$). The larger the mass finally grew the more severe the hydrops-associated symptoms became. Some of the separately tested, hydrops-associated symptoms were

stronger predictors of the mass size than others. Skin edema, ascites, and placentomegaly were prevalent with very large masses (in 61% to 83%), whereas pleural effusion and polyhydramnios did not occur as often with very large masses as the other three symptoms. They were also found in combination with smaller sized masses. A pericardial effusion was not associated ($p>0.4$) with the size of the mass at all (Table 4).

A hydrops fetalis was a very strong predictor of the early outcome ($p<0.001$). Individual hydrops-associated symptoms of ascites, skin edema, and placentomegaly were also strong predictors of the early outcome ($p<0.001$). The other symptoms of polyhydramnios, pleural effusion, and pericardial effusion did not consistently or independently of other hydrops-associated symptoms predict the early outcome ($p>0.06$ to $p>0.4$). Like the size of the mass, a hydrops, ascites, skin edema, and placentomegaly were significantly associated ($p<0.001$ to $p<0.05$) with mortality, prematurity, and lower 1- and 5-minute Apgar scores, as well as with early respiratory symptoms and the need for pre- or postnatal therapeutic interventions (such as a tumor operation, ventilatory support, and intensive care treatment). Eight of thirteen (62%) hydropic fetuses died due to TOP (3 cases), or after fetal surgery (3 cases), or due to spontaneous preterm delivery because of maternal contraindications from prenatal surgery (2 cases) (Tables 1 and 5).

Table 5.
Survival rate of 60 fetuses with cystic lung lesions – with or without a hydrops

	Prenatal survival	Survival between birth and 1 year of age	Survival between 1 and 13 years of age
Survival*	54 of 60	51 of 54	51 of 51
Death with Hydrops**	5	3	0
Death without Hydrops***	1	0	0

(* 5 survivors with hydrops included, ** 3 deaths due to TOP included, *** 1 death due to TOP included)

All five hydrops survivors (5 of 13 hydrops cases, 38%) required prenatal tumor resection and they exhibited severe early respiratory symptoms, necessitating more than 20 days of ICU treatment (5 of 5 cases) and prolonged ventilatory support for more than 20 days in three of the cases (3 of 5 cases) (Tables 3 and 4). The more advanced the hydrops, ascites, skin edema, or placentomegaly had been before birth the lower the 1- and 5-minute Apgar scores were at birth ($p<0.001$ to $p<0.01$), the more severe the early respiratory symptoms were after birth ($p<0.001$), and the longer the ventilatory support was used ($p=0.001$).

The 13 hydropic fetuses were compared with the 14 fetuses that had no obvious hydrops, but solitary ascites (3 mild), solitary pleural effusion (2 mild and 1 marked), or solitary pericardial effusion (7 mild and 1 marked). The association between a solitary effusion and a mass expansion or an unfavorable early respiratory outcome was weaker ($p<0.03$) than the association between a hydrops and the mass size or between a hydrops and the early respiratory outcome ($p<0.001$), although the association was stronger than for non-hydropic cases without solitary effusions.

In contrast to the unfavorable early respiratory outcomes of the children with prenatal hydrops, the final respiratory outcomes of the hydrops survivors were excellent. Similar to the prenatal size of the mass, a prenatal hydrops and hydrops-associated symptoms did not influence long-term outcomes ($p>0.3$ to $p>0.9$). All 5 survivors of advanced prenatal hydrops (coupled with very large masses) grew out of their initial severe early respiratory difficulties, and they were asymptomatic (4 of 5 cases) or had only minor respiratory symptoms (1 of 5 cases), 2 to 12 years later, at their final follow-ups (Tables 3 and 4).

5.3.4 The degree of the mediastinal shift correlated with the size of the mass and it was also a strong predictor of the early outcome

A mediastinal shift was observed in 51 (88%) of the 58 cases (data were not available in two cases: TOP case no. 42 and moderate sized lesion case no. 34). The mediastinal shift was categorized as overall marked in 18 (31%), overall moderate in 10 (17%), and overall mild in 23 (40%) of the 58 cases. In only 7 (12%) of the 58 cases, the mediastinum was not shifted. The mediastinum shifted to the side that was contralateral to the location of the lung lesion. There was, regarding the size of the lung lesion or the degree of the mediastinal shift, no side preference of the lesion and the contralateral shift ($p>0.5$). Of 59 lesions, 30 (51%) lesions were located on the left side of the thorax and shifted the mediastinum to the right, 26 (44%) lesions were on the right side, and 3 (5%) lesions were bilateral with no shift (no records of the location of the lung lesion of TOP case no. 42 were available).

The extension of the mediastinal shift significantly correlated with the size of the mass ($p<0.001$). A mediastinal shift appeared at a mean of 21.5 ± 3.0 weeks' gestation (17.6 to 33.6 weeks' gestation), which was about 1 week after the mean gestational age of the diagnosis of (very) large masses and about 1 ½ weeks before the mean gestational age of a potential hydrops development (see previous CHAPTERS 5.3.2 and 5.3.3). At the first diagnosis, the mediastinal shift was mild or moderate in 36 of 52 serially scanned fetuses, and it regressed in 53% (19 of 36) of these cases until the end of the prenatal observation. Ten of the 52 serially scanned cases had initially marked mediastinal shifts, but those shifts persisted as marked in 70% (7 of 10 cases). In total, the mediastinal shifts regressed in 38.5% (20 of 52 serially scanned cases), stayed the same in 38.5% (20 of 52

cases), and increased in 23% (12 of 52 cases). The change of the shift followed the growth pattern of the mass ($p=0.001$), which was described in detail in the earlier CHAPTER 5.3.2.

A higher degree of the mediastinal shift was associated ($p<0.001$) with a larger size of the mass, a higher chance of hydrops development, premature delivery, and a poorer early outcome with more severe early respiratory symptoms and a longer duration of ventilatory support, ICU treatment, or both. Of the 18 fetuses with a marked mediastinal shift, 89% (16 of 18 cases) ultimately had very large masses and 67% (12 of 18 cases) developed a hydrops. Or in other words, 89% (16 of 18 cases) of the ultimately very large masses and 92% (12 of 13 cases) of the hydropic fetuses were accompanied by marked mediastinal shifts. The survival rate of the fetuses with marked mediastinal shifts was 61% (11 of 18 cases), and all the survivors had severe early respiratory symptoms (11 of 11 cases) (Table 4). In contrast, the 30 fetuses with a mild or no shift had masses that were ultimately small or vanished in 57% (17 of 30 cases). None of them had a very large mass or developed a hydrops. Most of the children in that group were asymptomatic or only mildly affected early after birth (87%, 26 of 30 cases) (Table 4).

Again, as with the size of the mass or the development of a hydrops, the mediastinal shift was a highly significant prognostic factor of the early respiratory outcome ($p<0.001$), but not of the final respiratory outcome ($p>0.4$), which was excellent.

6. Discussion

6.1 Prediction of the outcomes

6.1.1 The set of prenatal early outcome predictors that this 60-patients-study disclosed, strikingly coincides with the predictor set generated by an extended statistical analysis of published data

The goal of my 60-patients-study was to research the natural history of fetal cystic lung lesions and how this history determines the postnatal outcome, in order to establish prenatal criteria to help counsel expecting parents of affected fetuses appropriately. Relying on the two participating centers' 14 years experience with fetal cystic lung lesions, such as CCAM and BPS, I performed a survey of 60 fetuses diagnosed with cystic lung lesions. To the best of my knowledge, this study presented here is unique regarding the large numbers of prenatal cases, the long follow-up interval of up to 13.1 years (mean follow-up age: 5.9 ± 3.3 years), and the comprehensive study of the prenatal ultrasonographic data to determine statistically significant predictors of the early and long-term outcomes. The equal gender distribution in this study of 31 female versus 28 male patients (1 TOP case was of unknown gender) argues against a bias in the studied fetal patient population. I consider this a result of my patient recruitment strategy, outlined in detail in CHAPTER 4.1.2 of the PATIENTS AND METHODS section. The results of this study show that the early respiratory outcomes of fetuses with cystic lung lesions are significantly associated ($p<0.001$) with the final size of the lesion, the development of a non-immune hydrops fetalis, and the mass- and hydrops-associated symptoms of mediastinal shift, skin edema, ascites, and placentomegaly. An ultimately

very large mass, a high degree of a mediastinal shift, and the development of a hydrops or symptoms of skin edema, marked ascites, and placentomegaly are significant predictors of a complicated early outcome, impaired by respiratory difficulties and prematurity. In rare cases only, a child may not survive the neonatal period. While the early respiratory outcome can be well predicted by the above-mentioned prenatal parameters, the long-term outcome cannot be predicted by any of the prenatal parameters at all, since in general, symptoms resolve in the neonatal period or in the first 2 years of life. The long-term outcome of children with fetal cystic lung lesions is excellent, as this study shows.

I compared the data of this 60-patients-study with the data of 49 clinical studies presented in the literature. The authors of the 49 studies examined the prenatal symptoms and outcomes in series with 10 or more fetuses with congenital cystic lung lesions. No other selection criteria were applied. Analyzing these studies published since 1985 by authors from 35 institutions (among them 5 multi-center-studies), I identified 1,442 fetal cystic lung lesion cases (Table 6 and Figure 6). I statistically analyzed the published data and searched for the most reliable prenatal predictors of the early outcome. As a conclusion, the development of a hydrops and the presence of a non-regressive, large lung lesion are the most frequently cited and reliable predictors of an unfavorable perinatal outcome (Table 7). The findings of my 60-patients-study coincide with the other authors' results, as discussed in detail below and compiled in Tables 6 and 7. Finally, the clinical implications of the entire study are the significantly improved pre- and postnatal management recommendations.

Table 6.
Extended literature analysis: 50 major published clinical series of fetal lung lesions

Study no.	First author [Ref.], Institution	Period, Follow-up interval	Cases	Postnatal surgery	Fetal treatment	Major associated anomalies	Mortality rate // TOP rate // Corrected mortality rate ***	Prenatal mass size regression [predictive value**** of mass size]	Hydrops [predictive value****]	Med. shift [predictive value****]	Poly [predictive value****]	Type of lesion [predictive value****]
1	**This study**, 2 center study: University of California, San Francisco (UCSF) & Ludwig Maximilian University, Munich, Germany (*b*d*e*f)	1988-2002 (some overlap), f/u: mean 5.9 yo, 1.3- 13.1yo	**60** (CCAM, BPS, Hybrid, BC*, BE*)	12x neonatal surgery (incl. 3 elective), 15x later surgery (2mo-4yo, incl. 9 elective)	10x fetal surgery (2 ND + 1 ID + 7 survivors), 3x shunt (incl. 1 hydrothx), 1x thoracocentesis (4 survivors)	8.3% [5 cases: Mayer-Rokitansky-Küster-Hauser syndrome (with R renal agenesis & vaginal atresia), albinism, Asperger syndrome, craniosynostosis, olivary nuclei dysplasia (TOP)]	15.0% (4 TOP, 4 ND, 1 ID @ 2 mo) // 6.7% // **5%**	35% (21, incl. 7 complete) [+]	**21.7%** (13 cases, incl. 3 TOP + 4 ND with 2 after fetal surgeries + 1 ID after fetal surgery + 5 fetal surgeries) [+]	85% (51, incl. 18 marked) [+]	36.7% (22, incl. 5 marked; excl. 1 oligo) [-]	12x type I, 17x type II, 21x type III (10 unkn.) [+]
2	**Lopoo** [99], UCSF	1992-1998 (some overlap), f/u: mean 39 mo, 4-77mo	**14** (BPS, Hybrid)	10x postnatal surgery (all elective)	2x shunt (for hydrothx) (all survivors)	7.1% [1 case: down syndrome]	0% // 0% // **0%**	28.6% (4, all complete) [-]	**14.3%** (2 cases, both fetal shunt) [+]	64.3% (9, incl. 3 severe) [-]	no info [n/a]	14x echogenic [+]
3	**Adzick** [5], 2 center study: UCSF & CHOP	1983-1997 (overlap), f/u: perinatal, except fetal surgery: 6mo-7yo	**175** (CCAM, BPS, Hybrid)	77x postnatal surgery	13x fetal surgery (4 IUD + 1 ND + 8 survivors), 8x shunt & 1x thoracocentesis' (incl. 3 hydrothx) (1 IUD + 8 surviv.')	1.7% [3 cases: multiple structural anomaly (TOP), down syndrome, tetralogy of Fallot]	27.4% (48 deaths: 16 TOP, others ND & IUD (incl. 5 fetal interv.) // 9.1% // **4.6%**? (some vague data)	24.6% (43?) [+]	**32.6%** (57 cases, incl. 12 TOP + 32 ND & IUD with 5 after fetal surg. & 1 after fetal shunt + 8 fetal surg. + 5 fetal shunts) [+]	deficient info [+]	deficient info [+]	deficient info [+]
4	**Adzick** [2], UCSF	1983-1994 (strong overlap), f/u: perinatal, except fetal treatment: 1-4yo	**52** (CCAM)	22x postnatal surgery	8x fetal surgery (1 ND + 2 IUD + 5 survivors) , 4x shunt (1 IUD + 3 survivors)	3.8% [2 cases: multiple structural anomalies (TOP), tetralogy of Fallot]	40.4% (6 TOP, 3 IUD, 12 ND) // 11.5% // **15.4%**	7.7% (4) [+]	**48.1%** (25 cases, incl. 5 TOP + 12 ND with one after fetal surgery + 3 IUD with all after fetal shunt/ surg.+ 5 fetal surg.) [+]	deficient info [n/a]	no info [+]	deficient info [n/a]
5	**Kuller** [88], UCSF	1985 - <1992 (strong overlap), f/u: perinatal	**22** (CCAM)	4x neonatal surgery	6x fetal surgery (1 IUD + 1 ND + 4 survivors), 1x shunt (IUD), 2x cyst aspiration (2 survivors)	4.5% [1 case: multiple structural anomaly (TOP)]	36.4% (4 TOP, 2 IUD, 2 ND) // 18.2% // **18.2%**	18.2% (4) [-]	**40.9%** (9 cases, incl. 2 ND with one after fetal surgery + 2 IUD with two after fetal shunt/ surgery + 5fetal surgery/shunt) [+]	deficient info [n/a]	no info [-]	8x micro-cystic, 14x macrocystic [n/a]
6	**Adzick and Harrison** [4], UCSF	1983-1990 (strong overlap), f/u: perinatal	**22** (CCAM)	12x postnatal surgery	2x fetal surgery (1 ND, 1 survivor), 2xthoracocentesis (2 survivors)	4.5% [1 case: tetralogy of Fallot]	45.5% (3 TOP, 7 ND) // 13.6% // **9.1%**	18.2% (4, incl. 3 partial) [+]	**40.9%** (9 cases, incl. 2 TOP, 7 ND including one fetal surgery) [+]	deficient info [+]	63.6% (14) [+]	12x macro-cyst., 10x microcystic [+]

7	**Adzick** [7], 2 center study: UCSF & The Swedish Hospital Medical Center, Seattle, Washington	<1985 (some overlap), f/u: perinatal	**12** (CCAM)	7x postnatal surgery	1x thoraco-centesis (survivor)	0%	50% (2 TOP, 4 ND) // 16.7% // **8.3%**	0% [+]	**41.7%** (5 cases, incl. 2 TOP, 3 ND) [+]	deficient info [+]	50% (6) [+]	7x macro-cyst., 5x microcystic [+]
8	**Crombleholme** [34], Children's Hospital of Philadelphia (CHOP) (*b*c)	1998-2001 (prospective study), f/u: perinatal	**58** (CCAM, Hybrid)	47x postnatal surgery or awaiting surgery (incl. 45 elective?)	7x fetal surgery (3 IUD + 2 ND + 2 survivors), 6x shunt & 4x cyst asp. (10survivors)	0% ? (major anomalies excl.?)	15.5% (7 IUD, 2 ND) // 0% (TOP excl.?) // **13.8%**	67.2% (39?) [+]	**32.8%** (19 cases, incl. 4 IUD & 2 ND with five after fetal surgery + 12 fetal treatment) [+]	no info [n/a]	no info [n/a]	17x type I, the others type II or III [+]
9	**Kamata** [81], Osaka University, Japan (*c *h)	1990-2004 (strong overlap), f/u: mean 6.9 yo, 1- 15.3yo	**23** (CCAM, BPS, BC*, BA*)	19x neonatal surgery, 3x infant surgery	1x shunt, 1x cyst aspiration (all survivors)	0%	4.3% (1 ND) // 0% // **4.3%**	no info [+]	**26.1%** (6 cases, incl. 1 ND + 2 fetal treatments) [+]	61% (14) [+]	no info [n/a]	deficient info [+]
10	**Usui** [143], Osaka University, Japan (*b *e)	1989-2001, f/u: perinatal, few until infant surgery	**28** (CCAM, BPS,BC*, BA*)	20x neonatal surgery, 3x infant surgery	1x shunt, 4x thoracocentesis (incl. 1 hydrothx) (all survivors)	0% (chromos. & cardiac anomalies excluded)	7.1% (2 ND, other anomalies excl.) // 0% (TOP excluded) // **0%**	10.7% (3, all complete) [+]	**53.6%** (15 cases, incl. 2 ND + 5 fetal treatments) [+]	no info [n/a]	39.3% (11) [+]	23x type I, 2x type II, 3x type III [+]
11	**Kamata** [80], Osaka University, Japan (*)	1989-1997 (all overlap), f/u: perinatal, 1x longer	**15** (CCAM, BPS, BA*)	9x postnatal surgery, 1x later surgery	2x cyst aspir.,1x thoracocentesis (for hydrothx) (all survivors)	0%	13.3% (2 ND) // 0% // **0%**	? [+]	**53.3%** (8 cases, incl. 2 ND + 3 fetal treatments) [+]	no info [n/a]	46.7% (7) [n/a]	9x type I, 4x type II, 2x type III [+]
12	**Kuroda** [90], National Center Child Health, Tokyo, Japan (*c)	2002-2005, f/u: perinatal	**28** (CCAM, BPS, CLE*, BA*)	6x neonatal surgeries, 7x elective surgery, [7x await surgery]	1x fetal surgery (IUD), 4x shunt (incl. 2 hydrothx) & 2x aspiration (both hydrothx) (6 survivors)	0%	14.3% (2 TOP, 1 IUD, 1 ID @ 2 mo old) // 7.1% // **7.1%**	17.9% (5) [+]	**7.1%** (2 cases, incl. 1 IUD after fetal surgery + 1 hydrothx-shunt) [+]	no info [n/a]	no info [n/a]	1x type I, 3x type III, 5x BPS (19 unkn.) [+]
13	**Truitt** [140], Brown University, Providence, RI	1997-2005, f/u: <18mo	**36** (CCAM, BPS, Hybrid, BC*, CLE*)	7x neonatal surgery, 23x infant surgery (incl. 22 elective with 14 endoscop.)	3x shunt (1 ND + 2 survivors)	0%	2.8% (1 ND) // 0% // **2.8%**	8.3% (3, incl. 2 complete - deficient info?) [n/a]	**8.3%** (3 cases, incl. 1 ND after fetal shunt + 2 fetal shunts) [+]	no info [n/a]	no info [n/a]	18x solid, 3x type I (15 unkn.) [+]
14	**Roggin** [123], Brown University & Hasbro Children's Hospital, Providence, RI	1995-1999 (some overlap), f/u: <16mo	**10** (CCAM, BPS, Hybrid)	4x neonatal surgery; 4x infant surgery (these elective)	1x shunt, 1x thoracocentesis (hydrothx) (all survivors)	0%	0% // 0% // **0%**	60% (6, all partial) [+]	**10%** (1 case, was shunt) [+]	70% (7) [-]	no info [n/a]	2x type I, 3x type II, 3x solid (2 unkn.) [+]
15	**Stöver** [133], Charite, Berlin, Germany	<2005, f/u: <1yo	**30** (CCAM, BPS)	3x neonatal surgery; 9x infant surgery (these elective)	no	7.1% [2 cases: vitium cordis (TOP); relaxatio diaphragmatica]	16.7% (5 TOP) // 16.7% // **3.3%**	43.3% (13, all complete) [+]	**13.3%** (<4 cases of “non immune hydrops of the lung”, all TOP) [+]	no info [n/a]	no info [n/a]	4x type I &II, 9x type III (17 unkn.) [-]
16	**Calvert** [25], John Radcliffe Hospital, Oxford, UK	1991-2001, f/u: 1-3yo	**28** (CCAM, BPS, Hybrid, BC*,BA*, BS*)	5x neonatal surgery, 12x infant surgery (these elective)	no	3.6% [1 case: trisomy 21 (TOP)]	25% (5 TOP, 2 ND) // 17.9% // **7.1%**	39.3% (11, incl. 4 complete) [+]	**10.7%** (3 cases, incl. 1 TOP + 1 ND) [+]	67.9% (19) [n/a]	no info [n/a]	deficient info [n/a]

17	**Illanes** [76], University of Bristol, UK	1994-2003, f/u: 6 mo-1yo	**48** (CCAM, Hybrid, BPS, CLE*)	23x infant surgery (all elective)	2x shunt (1ND + 1 IUD)	0%	18.8% (3 TOP, 4 IUD, 2 ND) // 6.3% // **4.2%**	45.8% (22, incl. 6 complete) [+]	**18.8%** (9 cases, incl. 1 TOP + 4 IUD with one fetal treatment + 2 ND with one fetal treatment + 2 mild pleural/pericardial effusion) [+]	67% (32) [+]	4% (2) [n/a]	24x macro-cystic, 24x micro-cystic (incl. 5 like BPS) [+]
18	**Ierullo** [75], St George's Hospital, London, UK	1998-2004, f/u: median 19 mo, 2-87mo	**32** (CCAM)	19x postnatal surgery or await surgery (mostly elective)	2x shunt (all survivors)	3.1% [1 case: aortic coarctation + small VSD (ID)]	12.5% (1 TOP, 2 ND, 1 ID @ 34 wks?) // 3.1% // **3.1%**	78.1% (25, all partial) [+]	**18.8%** (6 cases, incl. 1 TOP + 2 ND + 1 fetal shunt) [+]	84% (27, varying degrees) [-]	deficient info (>4?) [n/a]	25x micro-cystic, 7x macrocystic [+]
19	**Hsieh** [73], Chang Gung Memorial Hospital, Taipei, Taiwan	1990-2001, f/u: 7x: mean 62 mo, 44-79mo	**19** (CCAM)	0x surgery (despite 1 infant with bronchopneumonia)	no	15.8% [3 cases: situs inversus, TGA (TOP), VSD (TOP)]	63.2% (11 TOP, 1 ND) // 57.9% // **10.5%**	26.3% (5, all partial) [+]	**26.3%** (5 cases, all TOP) [+]	47% (9) [-]	37% (7) [-]	5x type I (one cyst), 5x type II (multiple cysts), 9x type III [-]
20	**Shanmugam** [131], Royal Hospital for Sick Children, Glasgow, Scotland, UK	1993-2003, f/u: longer, age?	**20** (CCAM, BPS)	4x neonatal surgery (all emergent), 10x infant surg. (mean 4.7 mo, all elective)	3x amniocentesis (all survivors)	0%	0% // 0% // **0%**	80% (16, incl. 6 complete) [+]	**0%** [+]	no info [n/a]	15% (3) [+]	5x type I, 4x type II, 5x solid (6 unkn.) [+]
21	**Achiron** [1], 2 center study: Tel Aviv University & Jerusalem's Hadassah University Hospital, Israel	1995-2003(?), f/u: longer, age?	**34** (CCAM, BPS)**	2x neonatal surgery, 1x neonatal bilat embolization (with CDH-correction) (all emergent)	1x shunt (for hydrothx) (survivor)	8.8% [3 cases: 2x gastric duplication cysts, 1x CDH]	14.7% (4 TOP, 1 IUD) // 11.8% // **2.9%**	55.9% (19, some complete) [+]	**5.9%** (2 cases, both TOP) [+]	no info [n/a]	no info [n/a]	29x solid, 3x cystic, 2x mixed [-]
22	**Davenport** [39], King's College Hospital London, UK (*a*b)	1995-2001, f/u: median 36 mo, 2–60mo	**67** (CCAM, BPS, Hybrid)	42x postnatal surgery (DOL 1-34 mo)	3x shunt (all survivors), 1x percutaneous intrauterine laser therapy (ND)	3% [2 cases: renal agenesis (TOP), superior vena caval obstruct. syndrome (ND)]	7.5% (1 TOP, 2 IUD, 2 ND) // 1.5% // **4.5%**	14.9% (10, incl. 2 complete) [+]	**10.4%** (7? cases, incl. 1 TOP + 2 IUD + 2 ND with one fetal laser + 2 fetal shunts) [+]	44.8% (30) [+]	no info [n/a]	35x macro-cystic, 5x mixed, 27x microcystic [+]
23	**Thorpe-Beeston and Nicolaides** [138], King's College Hospital London, UK	1984-1992, f/u: perinatal	**58** (CCAM)	14x neonatal surgery	5x shunt (all survivors)	12.1% [7 cases: trisomy 18 (TOP), multicystic kidneys (2 TOP), exomphalos (TOP), encephalocele (TOP), facial cleft (TOP), tracheoesophageal fistula with congenital heart disease (IUD)]	48.3% (22 TOP, 3 IUD, 3 ND) // 37.9% // **12.1%**	5.2% (3) [+]	**29.3%** (17 cases, incl. 14 TOP + 2 IUD) [+]	51.7% (30) [+]	10.3% (6, excl. 6 oligo) [+]	31x micro-cystic, 27x macrocystic [+]
24	**Lee** [94], Seoul National Uni-versity, South Korea	1996-2001, f/u: perinatal	**16** (CCAM, BPS)	1x neonatal surgery	no	0%	0% // 0% // **0%**	68.8% (11, incl. 10 complete) [+]	**6.3%** (1 case) [+]	88% (14) [n/a]	6% (1) [+]	8x macro-cystic 1x microcystic 7x solid [+]

25	**Pumberger** [119], University of Vienna, Austria	< 2003, f/u: 6mo-1yo, 1x 6yo	**36** (CCAM, BPS, Hybrid, BC*)	18x infant surgery (1mo – 1yo, incl. 14 elective),1x late surgery (6yo)	2x thoraco-centesis (incl. 1 hydrothx), 3x amniocentesis (incl. thoraco-centesis') (all survivors)	13.9% [5 cases: renal agenesis with ambiguous genitalia (TOP), esophageal atresia with craniofacial dysmorphism (TOP), small bowel hyperechogenicity (IUD), chorioid plexus cyst, mitral valve insufficiency]	16.7% (4 TOP, 2 IUD) // 11.1% // **8.3%**	30.6% (11, incl. 6 complete) [+]	**8.3%** (3 cases, incl. 1 TOP + 1 IUD + 1 amnio-centesis) [+]	36.1% (13) [+]	13.9% (5) [+]	6x type I, 6x type II, 12x type III, (incl. 6 BPS) (12 unkn.) [+]
26	**Golaszewski** [57], University of Vienna, Austria	1989-1996, f/u: mean 30mo	**14** (CCAM)	5x postnatal surgery (DOL 1-4mo)	3x shunt (1 ND + 2 survivors)	14.3% [2 cases: spina bifida (TOP), complex malformation with sirenomelia, ventricular septal defect, Potter's syndrome (TOP)]	35.7% (4 TOP, 1 ND) // 28.6% // **21.4%**	28.6% (4, all partial) [+]	**21.4%** (3 cases, incl. 1 ND after fetal shunt + 2 fetal shunts) [+]	64.3% (9) [+]	21.4% (3) [n/a]	6x type I, 5x type II, 3x type III [+]
27	**Gornall** [59], University of Leicester, UK	1997-2001, f/u: peirop, age?	**37** (CCAM, BPS)	16x postnatal surgery	2x cyst drainage, 1x shunt (all survivors)	8.1% [3 cases: hydronephrosis, 2x ventricular septum defects (1 TOP)]	8.1% (3 TOP) // 8.1% // **5.4%**	35.1% (13) [+]	**13.5%** (5 cases, incl. 1 TOP + 1 IUD + 3 fetal treatments) [+]	no info [n/a]	8.1% (3) [-]	11 type I, 5 type II, 18 type III (3 unkn.)[+]
28	**Duncombe** [48], University of Western Australia	1995-2001, f/u: median 265 days, max. 7yo	**21** (CCAM, Hybrid)	13x postnatal surgery (median 265days, incl. 12 elective)	1x cyst aspiration (TOP), 1x amnioreduction (survivor)	0%	23.8% (4 TOP, 1ND) // 19% // **4.8%**	33.3% (7, incl. 2 complete) [n/a]	**9.5%** (2 cases, incl. 1 TOP + 1 amnioreduction) [+]	52.4% (11) [n/a]	deficient info [n/a]	16x macro-cystic, 5x microcystic [n/a]
29	**Kähler** [79], Friedrich Schiller University Jena, Germany	1993-2001, f/u: 5x: mean 1.25yo, 2x >4yo	**12** (CCAM, BPS)	2x neonatal surgery	1x cyst aspiration (survivor), 1x amnioninfusion for anhydramn. (IUD)	8.3% [1 case: bilat renal agenesis (IUD)]	58.3% (6 TOP, 1 IUD) // 50% // **8.3%**	25% (3, incl. 2 complete) [+]	**25%** (3 cases, all TOP) [+]	83.3% (10) [-]	0% [n/a]	5x macro-cystic, 3x microcystic, 4x echogen [+]
30	**Blau** [15], Schneider's Children Medical Center, Petach Tikva, Israel	1995-2000, f/u: <24mo	**24** (CCAM, BPS, BC*, CLE*)	14x postnatal surgery (4-24mo, incl. 12 elective)	no	0%	0% // 0% // **0%**	29.2% (7, all partial) [+]	**0%** [n/a]	deficient info (some mild) [n/a]	no info [n/a]	13x cystic, 6x echo-genic, 5x cystic & echogen [+]
31	**Laberge** [91], 3 center study: Montreal Children's Hospital & University Hospital Edmonton & University of British Columbia Vancouver, Canada	1980-1990, f/u: perinatal	**48** (CCAM, BPS, Hybrid, BC*, CLE*)	> 27x postnatal surgery?	1x shunt (ND)	14.6% [7 cases: trisomy 18 (ND), laryngeal atresia & sirenomelia with renal - & gallbladder agenesis and caudal regression (TOP), congen. heart disease with imperf. anus and liver anomaly (TOP), malrotation with adrenal atrophia (ND), vertebral malformations with liver calcific. (IUD), pericardial window, bilat cleft,]	25% (7 TOP, 1 IUD, 4 ND) // 14.6% // **12.5%**	47.9% (23) [+]	**10.4%** (5 cases, incl. 1 TOP + 3 ND with one after fetal shunt) [+]	39.6% (19) [-]	29.2% (14) [-]	20x macro-cystic, 5x microcystic (23 unknown) [+]
32	**Neilson** [107], Montreal Children's Hospital, Canada	1980-1990 (strong overlap), f/u: mean 20mo, 8mo-4yo	**10** (CCAM, Hybrid)	8x postnatal surgery (DOL1-4 mo, incl. 3 elective)	1x cyst aspiration (ND)	27.3% [3 cases: laryngeal atresia & sirenomelia with renal - & gallbladder agenesis, caudal regression (TOP), congen. heart disease with imperf. anus, liver anomaly (TOP), bilat cleft]	50% (2 TOP, 3 ND) // 20% // **27.3%**	10% (1, partial) [+]	**40%** (4 ascites cases, incl. 1 TOP + 2 ND with one after fetal treatment) [+]	deficient info [+]	50% (5) [+]	6x type I, 2x type II, 2x type III [+]

33	**Monni** [104], 2 center study: Ospedale Regionale, Cagliari & University of Naples Federico II, Italy	<2000, f/u: >1 -4yo, only 2x >3yo	**26** (CCAM)	9x postnatal surgery, incl. 6 elective)	no	3.8% [1 case: renal agenesis (TOP)]	34.6% (9 TOP) // 34.6% // **3.8%**	11.5% (3, all complete) [+]	**7.7%** (2 cases, both TOP) [+]	57.7% (15) [-]	34.6% (9) [+]	13x micro-cystic, 13x macrocystic [+]
34	**Teodoro** [137], University of Naples Federico II, Italy	1994-1997 (some overlap), f/u: perinatal	**10** (CCAM)	2x postnatal surgery	no	10% [1 case: bilateral renal agenesis (TOP)]	70% (7 TOP) // 70% // **10%**	? [-]	**20%** (2 cases, both TOP) [+]	70% (7) [-]	no info [n/a]	3x type I, 3x type II, 4x type III [+]
35	**De Santis** [41], Catholic University Rome, Italy	1984-1999, f/u: 1mo-15yo	**17** (CCAM)	4x neonatal surgery, 4x later surgery	no	5.9% [1 case: occult bifid spine with sacrum agenesis)]	23.5% (2 TOP, 1 IUD, 1 ND) // 11.8% // **11.8%**	52.9% (9, incl. 3 complete) [-]	**11.8%** (2 cases, incl. 1 IUD + 1 ND) [+]	52.9% (9) [-]	11.8% (2) [-]	3x type I, 8x type II, 6x type III [+]
36	**Bunduki** [21], University of Sao Paulo, Brazil (*a*e*g)	1993-1999, f/u: >1yo	**18** (CCAM)	13x postnatal surgery (DOL 2-8 mo)	1x cyst aspiration (ND), 1x shunt (survivor), 1x amniocentesis (ND)	0%	33.3% (2 IUD, 3 ND, 1 ID @ 2mo old) // 0% // **11.1%**	16.7% (3, all partial) [+]	**38.9%** (7 cases, incl. 4 ND with 2x after fetal treatment + 2 IUD + 1 fetal shunt) [+]	61.1% (11) [-]	22.2% (4) [-]	7x micro-cystic, 11x macrocystic [+]
37	**Waszak** [147], Hospital Edouard Herriot of Lyon, France	1988-1997, f/u: perinatal, few until 1yo	**20** (CCAM, Hybrid)	18x neonatal surgery (incl. 6 elective)	no	5% [1 case: mild ventricular septum defect & moderate unilat. pyelectasis]	0% // 0% // **0%**	15%? (3?) [n/a]	**0%** [n/a]	5%? (1 signif.) [+]	0% [n/a]	11x macro-cystic, 5x microcystic (4 unkn.) [-]
38	**van Leeuwen** [144], University of Michigan (incl. 3 affiliated hospital), Ann Arbor, MI (*a)	1988-1998, f/u: mean 36.3 mo, 3mo-68mo, only 4x >3yo	**16** (CCAM, BPS, BC*)	4x neonatal surgery (all symptomatic), 4x infant surgery (all elective)	no	0%	0% // 0% (TOP excl.?) // **0%**	43.8% (7, all partial) [+]	**0%** [n/a]	25% (4, all signif.) [+]	12.5% (2) [n/a]	3x type I, 9x type II, 1x type III (3 unkn.) [n/a]
39	**Lacy** [93], Fetal Center Liverpool, UK	1991-1996, f/u: perinatal, 1x until 4yo	**21** (CCAM, BPS, CLE*, BA*)	6x neonatal surgery (all symptomatic)	no	4.8% [1 case: Fraser syndrome with laryngeal atresia, renal agenesis, cryptophtalmus (TOP)]	14.3% (2 TOP, 1 ID @ 2mo old) // 9.5% // **9.5%**	61.9% (13, incl. 9 complete) [-]	**0%** [n/a]	9.5% (2 marked & TOP) [+]	no info [n/a]	15x echo-genic, 6x cystic or mixed [+]
40	**Becmeur** [13], Hospital Hautepierre, Strasbourg, France	<1998, f/u: 1-6yo	**10** (BPS, Hybrid)	3x neonatal surgery (incl. 1 elective), 7x infant surgery (1-13 mo old, incl. 6 elective)	1x paracentesis (for ascites & poly),1x shunt (for hydrothorax) (all survivors)	30% [3 cases: pyloric stenosis & prune belly, hydrocephalus, aortic coarctation]	0% // 0% // **0%**	50% (5, all partial) [+]	**20%** (2 cases, both fetal treatment) [+]	deficient info [+]	deficient info [+]	10x highly dens [n/a]
41	**Dommergues** [46], Port-Royal & Necker Hospital, Paris, France	1987-1994, f/u: periop., mostly <5mo, max. 5yo	**33** (CCAM, BPS)	10x neonatal surgery, 10x later surgery	9x shunt (4 ND + 1 TOP + 4 survivors)	3% [1 case: porencephal with leucomalacia,ventriculomegaly (TOP)] (exclusion of chromosomal defects)	21.2% (3 TOP, 4 ND) // 9.1% // **18.2%**	54.5% (18, incl. 4 complete) [+]	**27.3%** (9 cases, incl. 3 TOP with one after fetal shunt + 2 ND after fetal shunt + 3 fetal shunts) [+]	57.6% (19) [+]	72.7% (24, incl. 5 major) [+]	11x type I, 15x type II, 7x type III [-]
42	**Revillon** [121], Port-Royal & Necker Hospital, Paris, France	1987-1992 (strong overlap), f/u: periop, 4x until 1yo	**32** (CCAM, Hybrid)	3x neonatal surgery (all symptomatic), 15x infant surgery (all elective)	4x shunt (1 TOP + 1 ND + 2 survivors)	9.4% [3 cases: 2x diffusely hypoechogenic cerebral cortex (2 TOP), Klinefelter (TOP)]	18.8% (5 TOP, 1 ND) // 15.6% // **12.5%**	40.6% (13, all partial) [+]	**18.8%** (6 cases, incl. 4 TOP with one after fetal shunt + 1 ND after fetal shunt + 1 fetal shunt) [+]	25% (8) [-]	50% (16, incl. 4 severe) [-]	12x type I, 15x type II, 5x type III [+]

43	**Dumez** [47], Port-Royal & Necker Hospital, Paris, France	1986-1990 (strong overlap), f/u: 4mo	**18** (CCAM)	9x postnatal surgery	3x shunt (1 TOP+ 1 ND + 1 survivor)	11.1% [2 cases: diffusely hypoechogenic cerebral cortex (2 TOP)], (excl. of chromosomal defects)	27.8% (4 TOP, 1 ND) // 22.2% // **16.7%**	16.7% (3, incl. 2 complete) [+]	**16.7%** (3 cases, all TOP with one after fetal shunt) [+]	50% (9) [+]	66.7% (12, incl. 3 severe) [+]	5x type I, 9x type II, 4x type III [-]
44	**Sapin** [128], Saint Vincent De Paul's Hospital, Paris, France	1985-1994, f/u: longer, age?	**18** (CCAM)	6x neonatal surgery (all symptomatic), 9x infant surgery (all elective)	no	0%	5.6% (1 TOP) // 5.6% // **0%**	27.8% (5, incl. 3 complete) [+]	**5.6%** (1 severe hydramnios, was TOP) [+]	>80% (incl. 12x at birth, 5 severe) [n/a]	22.2% (4) [-]	12x type I, 4x type II, 2x type III [+]
45	**Cacciari** [23], University of Bologna, Italy	1990-1995, f/u: mean 29 mo, 5mo-5yo	**16** (CCAM, Hybrid)	4x neonatal surgery, 5x infant surgery	no	0%	25% (3 TOP, 1 ND) // 18.8% // **6.3%**	18.8% (3, all complete) [+]	**6.3%** (1 case, was TOP) [+]	no info [+]	25% (4) [+]	11x type I, 6x type II, 0x type III [+]
46	**Miller** [103], Washington University, St Louis, Missouri (*)	1988-1995, f/u: median 26.5 mo, 4mo-6yo	**17** (CCAM, BPS, Hybrid, BC*)	4x neonatal surgery (all symptomatic), 8x infant surgery (all elective)	1x shunt (survivor)	11.8% [2 cases: complex malformation with bilat single forearm bones, ventral abdom wall defect (IUD), facial dysmorphism (IUD)]	29.4% (3 TOP, 2 IUD) // 17.6% // **11.8%**	41.2% (7) [+]	**23.5%** (4 cases, incl. 2 TOP + 2 IUD) [+]	76.5% (13, incl. 4 severe) [-]	17.7% (3, isolated) [-]	12x type I, 2x type II, 3x type III [-]
47	**Barret** [12], University of Toronto, Ontario, Canada	1992-1993, f/u: 6wks-6mo	**11** (CCAM)	2x neonatal surgery (all symptomatic)	no	9.1% [1 case: sacral neural tube defect (TOP)]	27.3% (3 TOP) // 27.3% // **9.1%**	27.3% (3, all complete) [+]	**9.1%** (1 case, was TOP) [+]	63.6% (7) [-]	no info [n/a]	6x cystic, 5x solid [-]
48	**Bromley** [18], General & Children's Hospital, Boston (*a)	1988-1994, f/u: perinatal, max. 10mo?	**23** (CCAM, BPS, Hybrid)	8x neonatal surgery (incl. 2 elective)	no	8.7% [2 cases: trisomy 18 (ND), trisomy 21 with hydrocephalus & abnormal kidney (TOP)]	39.1% (5 TOP, 2 IUD, 2 ND) // 21.7% // **17.4%**	34.8% (8, incl. 1 complete) [+]	**4.3%** (1 case, was IUD) [+]	65.2% (15, incl. 5 severe) [+]	30.4% (7) [+]	8x type I, 5x type II, 10x type III [+]
49	**McCullagh** [101], Children's Hospital Lewisham, London, UK	1991-1993, f/u: mean 25 mo, 9-41mo	**13** (CCAM, BPS, BA*)	7x neonatal surgery (incl. 5 elective), 2x infant surgery (all elective)	4x shunt (incl. 1 for hydrothx) (all survivors)	0%	0% // 0% // **0%**	15.4% (2, all complete) [-]	**0%**? [n/a]	84.6% (11) [-]	15.4% (2) [n/a]	4x type I, 5x type II, 4x type III [-]
50	**Budorick** [20], 2 center study: UCSD, San Diego & University of Colorado, Denver	1983-1990, f/u: DOL1-11mo	**14** (CCAM, BPS, Hybrid)	5x neonatal surgery, 1x infant surgery (this elective)	no	7.1% [1 case: multiple structural anomaly (ID)]	35.7% (2 TOP, 2 ND, 1 ID @ 3mo old) // 14.3% // **7.1%**	42.9% (6, incl. 3 complete) [+]	**21.4%** (3 cases, incl. 1 TOP + 1 ND + 1 ID) [+]	57.1% (8, incl. 6 marked) [+]	35.7% (5) [+]	3x type I, 3x type II, 8x type III [-]

Legend:
1. ***** Series of prenatal cases sorted by year & subsequent series from same institution // 2. Statistics: *a = Fisher exact test, *b = X2 – analysis, *c = Student's *t*-test, *d = *T*-tests of means, *e = ANOVA = One-way analysis of variance, *f = Bivariate correlation, *g = Kruskal-Wallis test *h = Linear & logistic regression (*2 studies did not specify their statistical tests and the others used descriptive statistics only) // 3. **** Predictive value of prenatal parameter: [+] = Predictor, [-] = No predictor, [n/a] = Not accessible data // 4. *** Correction of mortality rate by exclusion of deaths due to termination of pregnancies or avoidance of fetal intervention despite no other anomaly // 5. ** Alternative classification by Achiron [1]: Lung dysplasia type III ="Classic BPS", Type IV ="Classic CCAM" // 6. * Exceptional diagnoses (max. 2 cases per study): BC=Bronchogenic cyst, BA=Bronchial atresia, BE=Bronchiectasis, BS=Bronchial stenosis, CLE=Congenital lobar emphysema // 6. Deceased cases: TOP=Termination of pregnancy, IUD=Intrauterine death, ND=Neonatal death, ID=Infant death

Table 7.

Extended literature analysis*:
Attribution of prognostic values to prenatal parameters

Prenatal parameter	% predictive (no. of publications) [+]	% not predictive (no. of publications) [-]	% not applicable (no. of publications) [n/a]
Hydrops	90% (45)	0% (0)	10% (5)
Mass size	82% (41)	12% (6)	6% (3)
Mediastinal shift	40% (20)	28% (14)	32% (16)
Polyhydramnios	34% (17)	20% (10)	46% (23)
Type of lesion	68% (34)**	20% (10)	12% (6)

* Inclusion of the 50 published clinical series of Table 6 (my 60-patients-study included)

** Divergent predictions made upon the type of the lesion:
8 times: "type I/ macrocystic is unfavorable"; 6 times: "type I/macrocystic is favorable"; 2 times: "type II is unfavorable"; 2 times: "type II is favorable"; 8 times: "type III/ microcystic is unfavorable"; 13 times: "type III/ microcystic/ echogenic is favorable"; 7 times: "CCAM is unfavorable"; 3 times: "BPS/ hybrid is favorable (without a hydrothorax)"

6.1.2 The size of the mass is the crucial pivotal point of the early outcome and it requires serial observation due to its non-static character

The size of the cystic lung lesion is not a static parameter. Most masses change their sizes during pregnancy. In this 60-patients-series, 40% of the fetal masses regressed, 25% increased, and only 35% kept the same relative size during the prenatal observational period. Within the last 6 years, the published regression rates are in the range of 8 and 80% with a mean regression rate of 39 ± 22% (Table 6). This is in accordance with the above mentioned figures of my study. Interestingly, solid appearing, Stocker type III lesions are reported to regress more often and result in a better outcome than other lesion types, as discussed in CHAPTER 6.1.4. Attributable to the size changes, the initial size of the mass is not useful for predicting the outcome. Miller *et al.* [103] demonstrate no significant difference in clinical outcome based on the initial size of the

lesion. However, I discovered different growth patterns in different mass size categories. Initially large or moderate sized masses frequently changed their sizes and were of no value in predicting the outcome. Masses with sizes initially described to be at the extreme low (very small) or high (very large) end of the size scale were more likely to maintain the same size until the end of the prenatal observational period. Mass sizes with these initial measurements predicted the early outcomes as well as the final mass sizes. A diagram in Usui *et al.* [143], outlining the initial mass size versus the final mass size, reflects the above described findings of my study. Interestingly, I observed one exception to that rule. One of the cases of my study, an initially small macrocystic Stocker type I lesion, grew rapidly to a very large mass until the pregnancy was terminated (case no. 59 of Tables 1 and 3). Crombleholme *et al.* [34] also observed that small Stocker type I lesions may grow abruptly to hazardous large masses, attributable to rapid fluid accumulation within a dominant cyst. Having this exception in mind and taking into account all considerations mentioned above, it becomes clear that in general, the initial size of the cystic lung lesion is not a reliable outcome predictor.

A significant change in mass size typically occurs during a narrow time frame. It can be divided into two phases, a period of critical mass size increase, followed by a period of mass size regression. The critical period of mass size increase for maximal large or very large lesions in my series was between 19 and 27 weeks' gestation, with a mean increase age of 22.3 ± 1.5 weeks' gestation. The Adzick group of the Children's Hospital of Philadelphia (CHOP), USA, also reports significant progressive growth between 20 and 26 weeks' gestation, with a peak growth at 25 weeks' gestation and a plateau of the growth at 26 to 28 weeks' gestation [5, 34]. Following the period of mass

size increase, fetal cystic lung lesions may regress, even if they reached a large size [5, 91, 103]. Regression of maximal large and very large masses was observed in my series at a mean of 27.6 ± 3.7 weeks' gestation. In agreement with the findings of my study, Budorick *et al.* [20] in 1992 describe in one of the earliest studies on fetal cystic lung lesions, the regression of six, probably large lesions at a mean gestational age of 27.8 ± 5.7 weeks. The most recent study on this issue, from the Jennings group [89] of the Children's Hospital Boston, USA, demonstrates in a series of 12 large fetal CCAMs that again, the peak dimension is reached at 25.3 ± 3.6 weeks' gestation, and a decrease of the CCAM mass volume (relative to the thoracic cavity volume) occurs by 25 to 30 weeks' gestation. Different from the larger masses, I observed that the non-critical, small or moderate sized masses regressed about 3 mean gestational weeks later, at 30.5 ± 3.8 weeks' gestation. Accordingly, mass size regressions are reported in the literature after 28 weeks' gestation [34] and at a mean menstrual age of 30.4 ± 1.7 weeks' gestation [94] in series including small as well as large masses. Attributable to their non-static character, fetal cystic lung lesions that grow to large sizes require close serial ultrasonographic surveillance, at least prior to potential regression and during the critical period of mass size increase and potential hydrops development between 18 and 29 weeks' gestation.

The size of the lesion in proportion to the size of the fetus (relative mass size) and not the absolute size of the mass is the measure according to which intra- or inter-individual case comparisons or outcome prognoses have to be made. The estimation of the fetal mass size (whether small, large, increased, or decreased) should be based on relative measures. In order to account for fetal growth, Lee *et al.* [94] consider the mass volume (calculated with the formula: anteroposterior height x width x craniocaudal length

x π/6) not to have regressed until the volume becomes less than 50% and not to have increased until the volume exceeds 150% of the initial volume. Crombleholme *et al.* [34] created a more precise, semi-quantitative size-associated dimension: the CCAM volume ratio (CVR). This measurement is helpful in predicting prenatal hydrops development. To normalize for gestational age, the CVR is the tumor elliptic volume (calculated with the formula: maximal length x width x height x 0.52) divided by the head circumference of the fetus. A CVR >1.6 at presentation predicts an increased risk of hydrops development, with a positive predictive value (PPV) of 75%, whereas fetuses with a CVR <1.6 are at low risk of developing a hydrops (PPV=83%). Another size-associated, straightforward measurement for predicting hydrops development is the mass to thorax ratio (MTR), as published by Vu *et al.* [145]. To adjust for fetal size, the MTR compares the transverse diameter of the mass to the transverse diameter of the fetal thorax, at the level of the 4-chamber view of the heart. An MTR value >0.6 is significantly associated with a hydrops development (PPV=74%). Miller *et al.* [103] calculated a similar dimension by dividing the cross-sectional area of the lesion by the cross-sectional area of the fetal thorax, from which the heart volume is excluded. As a converse dimension of the mass size and an indicator of pulmonary hypoplasia and fetal compromise, Kamata and Usui *et al.* [80, 81, 143] formulated the lung to thorax ratio (L/T), which is the measurement of the remaining normal bilateral lung area divided by the thorax transverse area, at the level of the 4-chamber view of the heart. Fetuses with no increase in L/T during pregnancy and a final L/T of <0.25 are at the highest risk of hydrops development (PPV=100% in their first series). They also showed in a second study that the L/T correlates with postnatal decrease in lung ventilation and perfusion [81]. In my study, the relative size of the mass

was addressed as follows: The size was determined by the examining ultrasonographer, and it was categorized into four size groups, regarding the proportion of the mass to less or more than one- or two-thirds of the fetal hemithorax. This approach is described in detail in CHAPTER 4.2.3 of the PATIENTS AND METHODS section and in Lopoo *et al.* [99]. The assignment to a particular size category in my study allowed the prediction of the early outcome, including the prediction of hydrops development, severity of early respiratory symptoms, and whether or not fetal or neonatal surgical treatment is required (with a PPV in the very large mass size group of 72%, 100%, and 100%, respectively). The early outcome findings are further discussed in detail in the last paragraph of this CHAPTER 6.1.2. The Dumez group [46, 47, 121] and van Leeuwen *et al.* [144] categorized the lesions into similar size groups, as they defined the extension of the lesion in the hemithorax as <50%, equal to 50%, >50%, and 100% (equals bilateral). The authors conclude that cases with a mass size <50% are at low risk of developing fetal complications and postnatal pulmonary sequelae, whereas cases with masses >50% have a higher risk of being symptomatic and requiring postnatal surgery. In a more simplified approach than in my study, Bromley *et al.* [18] classified the lesions into only two size groups: (a) lesions affecting parts of the lung, or (b) lesions affecting the entire lung, based on the presence of sonographically visible, adjacent ipsilateral lung tissue. Even with this more simple distinction into only two size groups, they could demonstrate that the mortality rate in the group with the entire lung involved is significantly higher compared to the other size group. Only in the course of my study, more standardized, objective size measures were introduced, such as the above-mentioned CVR, MTR, or L/T. Based on precise mass size measurements and normalized for fetal body size, these

measures are not only useful for intra- or inter-individual case comparisons within one series, but also beneficial for inter-study comparisons of different series. However, the approach with a 4-size-group classification in my 60-patients-study does not alter any conclusion, as reconfirmed by the results of the study on the MTR measure from Vu *et al.* [145].

The fetal lung tumor, depending on its size, causes the mediastinum to shift to the contralateral side. The results of my 60-patients-study show that the degree of the mediastinal shift significantly correlated with the extension of the mass ($p<0.001$), and it strictly followed the growth pattern of the mass (Table 4). The ultimate degree of the mediastinal shift was as prognostic ($p<0.001$) of the early outcome as the final size of the mass. In support of my observation, authors who measured the different degrees of the mediastinal shift and the potential shift changes came to the same conclusion [18, 39, 46, 76]. Studies that focused on the initial mediastinal shift of moderate sized masses ascribe no prognostic value to the mediastinal shift. This can be explained by the tendency of moderate sized masses to change their size during pregnancy, causing a change of the extent of the shift and herewith a change of the outcome prognosis [91, 103] (Tables 6 and 7). In one series, the mediastinal shift became insignificant as a prognostic factor, because several very large masses with poor outcome did not cause any mediastinal shift due to bilateralism [21]. Only unilateral masses cause mediastinal shifts. The possibility of determining the degree of a mediastinal shift facilitates the indirect quantification of the mass size. Therefore, the mediastinal shift can be used as an additional useful predictor of the early outcome in fetuses with unilateral masses.

The most crucial factor affecting the early outcome is the final or maximal size of the cystic lung lesion. The prenatal course, as well as the early and interim postnatal course, can be reliably predicted by the final or maximal mass size. In this study of 60 fetuses, I showed that the larger the mass grew the more likely ($p<0.001$) prenatal complications, postnatal complications, or both occurred (Tables 1, 3, and 4). Fetuses with ultimately very large masses were at high risk of developing a fetal hydrops (PPV 72%), being born prematurely (PPV 89%), and having severe early respiratory symptoms (PPV 100% of the survivors). They required aggressive pre- or postnatal treatment or both. Mortality (TOPs excluded) occurred rarely and exclusively in cases with very large masses in association with a hydrops. In contrast, fetuses with ultimately small sized masses were asymptomatic (70%) or only mildly affected (30%) after birth. As summarized in Tables 6 and 7 and in agreement with the findings of my study, 82% of the authors think that the size of the mass is an important predictor of the early outcome. Unfortunately, most authors cited in Table 6 did not define the mass size, except for the authors of studies numbers 1, 2, 8, 9-11, 24, 38, 41-43, 46 and 48. Their work was discussed above in the third paragraph of this CHAPTER 6.1.2. Few of the authors who did not define the mass size described bilateral masses to be in general of poor prognosis [21, 73, 79, 119, 138]. However, this is only true if the size of the combined bilateral masses is very large and does not regress. As a caveat, a very large unilateral mass, expanding from one side of the fetal thorax to the opposite side, could also be misdiagnosed as to be bilateral [48], as demonstrated in Figure 2. Bilateralism and tumor size are not linked. One bilateral mass in my series was ultimately very large and of poor outcome, whereas two other bilateral masses regressed with a good outcome, similar to

cases described by other authors [64, 128]. Six (12%) of the fifty publications cited in Tables 6 and 7 (study numbers 2, 13, 34, 35, 39, and 49) do not assign any predictive value to the lesion's size, because the authors only examined the initial size of the lesion, or they only vaguely described the lesion's size or the outcome criteria. As emphasized previously, accurately defined mass size groups and outcome parameters are a prerequisite for the determination of the (statistically significant) prognostic value of the lesion's final size. Most studies examined the perinatal outcome as the outcome endpoint and assessed hydrops development, survival rate, and requirement of pre- or postnatal surgery, as outlined in Table 6. I recorded additional parameters and showed that an early gestational age at birth, low 1- and 5-minute Apgar scores, and a long time period of oxygen requirement, ventilatory support, intensive care treatment, and (re-) hospitalizations correlated with the presence of a large mass and, herewith, with the need for aggressive surgical treatment (Table 2.1). The correlation between the four mass size groups and the early respiratory symptoms categorized into four severity groups is depicted in Tables 3 and 4. Few other authors also examined some additional early outcome parameters and came up with similar results, although with smaller patient cohorts than my cohort [34, 80, 103, 131, 143]. Kamata and Usui *et al.* [80, 143] additionally observed a significant correlation between the mass size (as defined by the maximal L/T) and the preductal alveolar-arterial oxygen gradient (A-aDO2) of the neonates under mechanical ventilation. They also found all neonates with a severe clinical course to have persistent pulmonary hypertension of the newborn (PPHN) as diagnosed using echocardiogram and pre- and postductal blood gas analyses. No PPHN was observed in mildly affected neonates. I further investigated non-respiratory problems

and found that early and prolonged difficulties with feeding, weight gain, and GERD were prematurity-associated problems in children with large fetal masses and after fetal hydrops. Prematurity is reported to significantly occur in fetuses with large masses [34, 91] and in hydropic fetuses with or without fetal treatment [5, 21, 25, 76, 143]. In this 60-patients-study, fetuses with very large masses but no hydrops were born at a mean gestational age of 35.6 ± 4.1 weeks. Those with signs of a hydrops were born already at a mean of 31.2 ± 3.6 weeks' gestation and had severe early respiratory symptoms when they survived. Prematurity is influential in early respiratory and non-respiratory morbidity, as well as in early mortality. The long-term outcome analysis is as important as the early outcome analysis. I succeeded in following-up with the children over a very long time period, which to the best of my knowledge has not been done before in a large patient cohort. I compared the early outcomes with the long-term outcomes and surprisingly, a disadvantageous early outcome did not lead to an unfavorable long-term outcome, as discussed in detail in CHAPTER 5.2.4 and 6.1.6. As this study has shown so far, the pivotal point for the antenatal, perinatal, and interim early outcomes is the fetal mass size. The mass size, which preconditions all other fetal symptoms, requires close ultrasonographic surveillance, at least during the critical period when the size increases.

6.1.3 First signs of a hydrops in fetuses with large lesions mark the beginning of serious complications starting before birth, but they can be averted with fetal treatment

A hydrops fetalis develops with high probability if the size of a large lesion exceeds a size the fetus cannot manage without cardiovascular decompensation. In this

60-patients-study, 72% of the fetuses with very large masses developed a hydrops. The reported positive predictive values for hydrops development in fetuses with large masses exceeding the threshold of a CVR of 1.6 and an MTR of 0.6 (as discussed in the previous CHAPTER 6.1.2) are 75% and 74% respectively [34, 145], similar to my results. On average, hydrops evolve in the fetal lung lesion population in 18.5 ± 14.7% of the cases. This figure was calculated from the published rates of hydrops development that have been disclosed in the series of Table 6, and those series were all of different degrees of severity regarding the symptoms of the patients. My 60-patients-series also represents a cohort of fetal CCAM and BPS patients with symptoms of different degrees of severity. I determined a hydrops development rate of 21.7%, which is similar to the rate calculated from the published data. In my series, the critical period of hydrops development, at 23.0 ± 3.2 mean gestational weeks, followed 1 week after the mean gestational week of mass size increase for very large masses, as described in the previous CHAPTER 6.1.2. This coincides with the observation of Crombleholme *et al.* [34], who report that a hydrops develops before the mass reaches its growth plateau at 26 to 28 weeks' gestation. The significant mass effects on the heart and the mediastinal structures of rapidly growing enlarged lung tumors cause fetal hydrops. As shown in the sheep model, the inflation of an implanted intrathoracic tissue expander results in an elevation of the central venous pressure, causing a hydrops [122]; and an increase of the fetal venous pressure of the jugular vein reduces the thoracic duct lymph flow, causing skin edema [17]. It is irrelevant whether the space occupying process involves an extending solid mass (such as a CCAM type III or II, or a BPS), a fluid accumulation in a single cyst of a mass (such as a CCAM type I [34], or a bronchogenic cyst), or a fluid accumulation in the pleural

cavity (causing tension hydrothorax in BPS cases [99]). What is relevant is the large size and rapid progression of the space occupying process in the fetal thorax. Further, a hydrops can also result from an anomalous venous drainage of large lesions via significant intrapulmonary arterio-venous shuns, causing cardiac decompensation and central venous congestion [1]. Why every very large mass does not cause a hydrops is not known, but what I found is that the larger and faster the mass grows or the fluid accumulates in the thorax, the higher the risk of developing a hydrops.

The signs of a hydrops are indicators of a condition threatening the fetus' life, already before birth. The natural history of untreated hydropic fetuses is grave. My extended statistical analysis of the series that are summarized in Table 6 revealed that 73.4% (83 of 113 cases) of the untreated hydropic fetuses died (Figure 6). Due to this alarming and unambiguous number of fatalities, a hydrops has become known as the most useful predictor for an unfavorable early outcome of fetuses with lung lesions [5, 34, 39, 46, 76, 91]. In 90% of the publications, summarized in Tables 6 and 7, authors convincingly show that a hydrops is an important predictor of the early outcome. In the remaining 10% no hydrops were observed. However, the mean overall mortality rate of 67% (199 of 297 hydrops cases) is an overestimation of the true mortality rate in hydropic fetuses. This was shown with the extended statistical analysis of all published series summarized in Table 6 and Figure 6. Of the 199 deceased hydropic fetuses, 81 fetuses (40.7%) died because the pregnancy was terminated, and an additional 83 fetuses (41.7%) did not survive because prenatal treatment was not attempted (Figure 6).

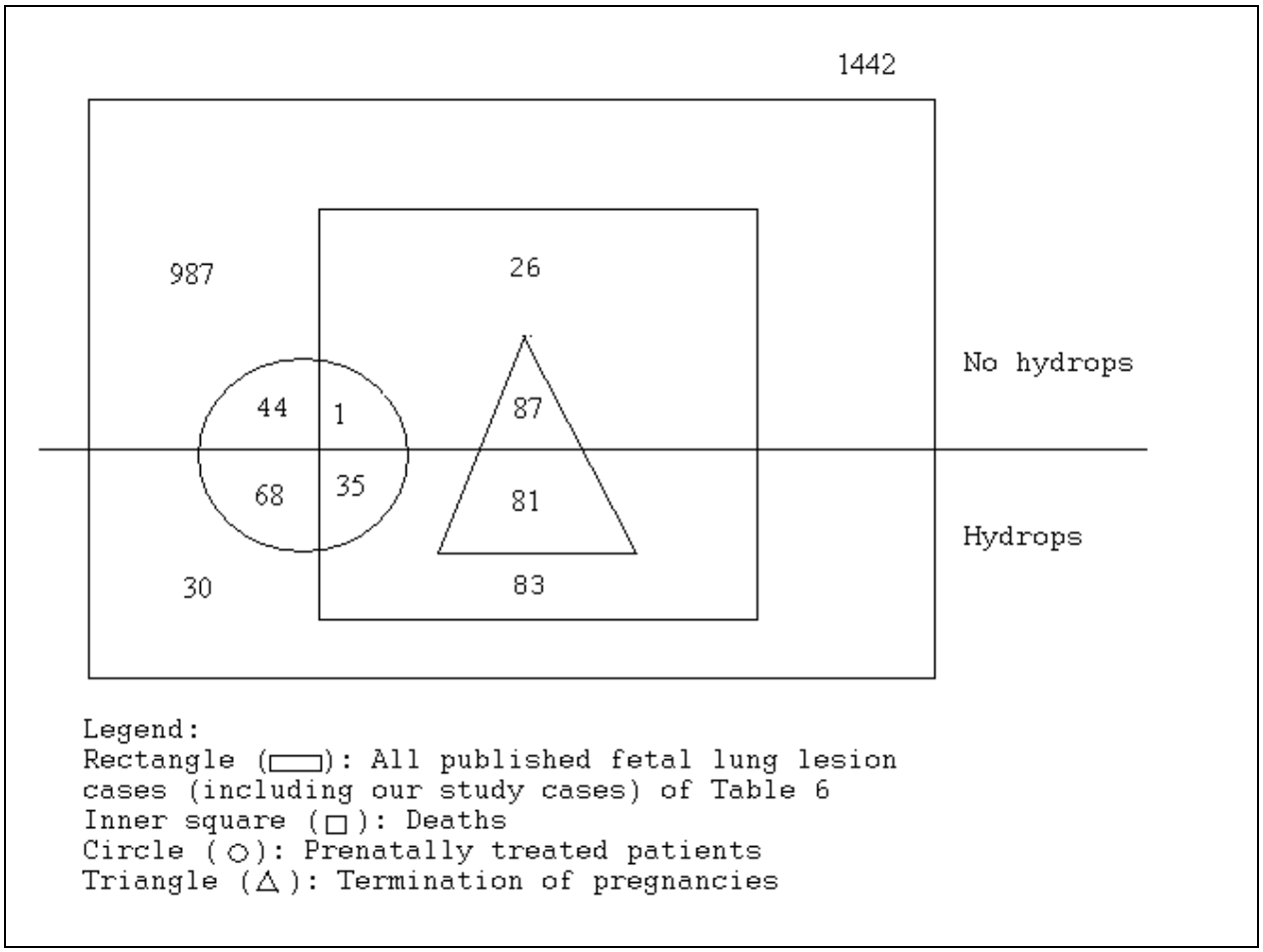


Figure 6. Extended literature analysis: surviving and non-surviving fetuses with lung lesions, with or without a hydrops, prenatally treated or not treated.

The true mortality rate of hydropic fetuses is obscured by the high number of terminated pregnancies [73, 104, 138] and the lack of fetal treatment [20, 25, 41]. The rate of hydropic fetuses who passed away in my 60-patients-series (61.5%, 8 of 13 hydropic fetuses) was also disproportionately high due to 3 terminations of hydropic pregnancies and 2 prenatally untreated hydropic cases. The statistical analysis of the data of all major published series generated an overall “true hydrops mortality rate” of 26.3% (35 of 133 hydrops cases), after the exclusion of TOPs and prenatally untreated expired

cases (Table 6 and Figure 6). In a recently published survey from the UCSF Medical Center, Grethel *et al.* [62] report the neonatal survival rates for (i) non-treated non-hydropic fetuses, (ii) treated non-hydropic fetuses, (iii) treated hydropic fetuses, and (iv) non-treated hydropic fetuses with CCAM or BPS (after exclusion of TOPs) to be (i) 98.5%, (ii) 85.7%, (iii) 56.7%, and (iv) 0%, respectively. These results are largely congruent with the results obtained from the extended statistical analysis of the published data (from 1985 to 2007) of (i) 97.4%, (ii) 97.7%, (iii) 66.0%, and (iv) 26.5%, respectively (Figure 6). The only exception is a higher percentage of surviving untreated hydropic fetuses in the analyzed published series, compared to the studies of Grethel's *et al.* and myself. In my series none of the hydropic fetuses survived without invasive fetal treatment from 1988 to 2002, as well as in Grethel's *et al* series from 1991 to 2006 (the series partly overlapped), whereas 26.5% (30 survivors among 113 untreated hydrops cases) survived in the reported literature (Table 6 and Figure 6). In the survivors, spontaneous improvement of the hydropic symptoms mostly occurred early in the third trimester [46, 75, 80]. Other authors not included in Table 6 also report remarkable spontaneous regression of very large masses followed by the improvement of a hydrops [36, 56, 60, 69, 89]. The mechanism of the spontaneous regression is not fully understood. True mass regression has to be distinguished from the proportional mass size reduction that occurs due to fetal growth and gradual augmentation of the surrounding normal lung tissue, while the lesion itself remains stable. Plausible explanations of true tumor shrinkage include: involution of the lesion due to the outgrowth of the blood supply or the obstruction of the vascular pedicle, decompression of fetal lung fluid through abnormal channels, and spontaneous correction of an underlying bronchial

obstruction within the lesion [1, 94, 100, 103]. Mass regression and improvement of hydropic symptoms point to a favorable outcome. However, it is premature to assume that the fetus is safe when hydropic symptoms disappear after fetal treatment or even if they disappear spontaneously. Although rare, serious perinatal complications are reported despite prenatal hydrops improvement [91, 97, 102, 149]. The early onset of a regression of the mass size and the hydrops seems to be the key to a favorable outcome. In the reported cases with good outcome, fetuses showed signs of a regression prior to 30 weeks' gestation, whereas after 31 weeks' gestation, most fetuses with late observed regressions experienced severe complications due to pulmonary hypoplasia, prolonged cardiovascular compromise, or both. A lingering untreated hydrops is a dismal situation for a fetus with a lung mass, and it justifies fetal therapeutic intervention.

Early recognition of signs of a hydrops and prompt therapeutic fetal intervention are crucial for successfully treating severely affected fetuses with cystic lung lesions. At the UCSF Children's Hospital as well as at the CHOP, fetal treatment specialists, like Michael R. Harrison and Scott N. Adzick [34], advise against delaying fetal therapy. Hoping for spontaneous hydrops resolution, even though it could eventually occur, endangers the fetus's life. The three unsuccessfully operated fetuses in my study who passed away had a fetal tumor resection done after 28 weeks' gestation and the hydrops was far advanced in all of them. All other ten successfully operated fetuses who achieved a good outcome, except for one case (a fetal shunt case), were operated on much earlier at a mean gestational age of 24.4 ± 2.1 weeks. Timely fetal therapeutic intervention increases the chance of survival for hydropic fetuses with cystic lung lesions.

Established fetal therapeutic interventions for cystic lung lesions are: (serial) aspirations or shunts, to drain rapidly enlarging cysts or tension hydrothoraxes, and open fetal surgery to resect very large tumors. Many of these interventions have been successfully performed since the pioneering first fetal thoracotomy and pulmonary tumor resection in 1990 by Harrison *et al.* [66] and the first fetal thoracocentesis and pulmonary cyst shunting in 1987 by Nicolaides *et al.* [109]. From 20 different fetal treatment centers (Table 6), I analyzed the surgical fetal intervention performances and the success rates are as follows: Of 148 prenatally operated fetuses, 112 survived upon cyst aspirations, shunting, and tumor resection. That results in an overall fetal intervention success rate of 76%. When limiting the focus to 103 hydropic fetuses after therapeutic fetal interventions (148 prenatally operated cases minus 45 non-hydropic cases), and when discriminating between cyst aspirations or shunting versus tumor resections, I calculated a success rate for hydropic fetuses of 78% (46 survivors of 59 cases) for aspirations or shunting versus 55% (24 survivors of 44 cases) for tumor resections. These results correspond with the most recent published outcome data on *in utero* therapy from the CHOP [152] and show that fetal therapeutic interventions are successful in saving hydropic fetuses. Early and effective mass volume reduction and timely resolution of a hydrops are crucial for a favorable outcome after fetal treatment. The group from Philadelphia observed hydrops resolution in the survivors 1 to 2 weeks postoperatively, which is in agreement with the experiences at the UCSF Medical Center and the findings of my study. Noteworthy is the fact that the premise for a successful fetal shunt therapy with an improved survival rate is an effectively functioning and long lasting shunt [108, 152]. However, even if the fetal therapeutic procedure is successfully accomplished, there may be postoperative

complications to be considered. A sudden thoracic decompression after the resection of a large lung mass may lead to intra-operative hemodynamic collapse, bradycardia, and fetal loss. This might require specific treatment adjustments to save the fetus [152]. For this case, the underlying pathophysiological mechanism is most likely the reverse effect of the above-mentioned mass effect of hydrops causing, rapid progressing masses. The most common and difficult to handle complications after fetal surgery are preterm labor (PTL) and premature rupture of membranes (PROM), which often result in premature delivery, as described in CHAPTER 5.2.3 of the RESULT section and in our published case report of PART II of this doctoral thesis. For this reason, fetal surgery was poorly received in Europe, in contrast to Northern American practices. Since the late 1990s, new minimally invasive, fetoscopic treatment options have been developed and, not until then were fetal surgical programs introduced in Europe to promote these techniques [44]. Thereafter, fetal (serial) aspiration and shunt interventions were increasingly performed in Europe. However, open fetal surgery remains to the best of my knowledge almost nonexistent in Europe, in spite of advanced, postoperative tocolytic management and despite the success rates that are reported by respected American fetal treatment centers.

In conclusion, the survival rate of hydropic fetuses with large cystic lung lesions can be significantly improved with timely fetal therapeutic intervention, preventing prolonged, irreversible damage to the fetus. Moreover, it seems advisable to also operate on non-hydropic fetuses with significant space-occupying lesions to prevent pulmonary hypoplasia, although further investigations need to be performed.

6.1.4 Marked ascites and the type of the lesion are, in contrast to polyhydramnios, independent outcome predictors

The results of my 60-patients-study show that marked ascites were predictive of the early outcome ($p<0.001$), even in cases in which they were not associated with a hydrops as classically defined by Evans [51]. Goldstein [58] suggests that the presence of solitary ascites is sufficient to diagnose the presence of a hydrops. Other authors regard solitary ascites in combination with polyhydramnios as hydrops [23, 107, 143]. A modified hydrops definition was also applied to two of my study cases which had marked ascites combined with placentomegaly and polyhydramnios. It should be emphasized that it isn't ascites alone, but the degree of the ascites, that justifies treating these cases as classically defined hydrops cases. All marked ascites in my series worsened and complicated the outcome, while 2 out of 3 mild ascites resolved. The resolution of ascites was observed by others, in cases of mild degrees of ascites or in the absence of further hydrops-associated symptoms [4, 21, 91, 119]. A mild solitary ascites is, as much as mild solitary pleural effusion or pericardial effusion, not an indicator of an unfavorable outcome. However, marked progressing ascites, especially in combination with polyhydramnios, is a predictor of an unfavorable outcome, as much as a classic hydrops.

Polyhydramnios is a controversially discussed outcome parameter. Of the studies included in Tables 6 and 7, 34% assign a prognostic value to polyhydramnios, 20% refrain to do so, and 46% do not address this issue. However, the authors consent to one issue: Polyhydramnios is a prognostic factor of the outcome if combined with hydrops, marked ascites, or both [4, 20, 94, 104, 143]. Solitary polyhydramnios can be transient [91, 128]. As the fetal lung lesion regresses, solitary polyhydramnios, as much as other

solitary fetal effusions, may resolve. This 60-patients-study showed that the degree of a polyhydramnios was significantly associated with the fetal lung lesion size and with fetal hydrops ($p<0.005$). Marked and moderate polyhydramnios were seen in very large masses (with only one exception), whereas mild poly was also found in mildly affected fetuses, and it regressed in three of them (Table 4). In summary, polyhydramnios is not a reliable outcome predictor independent of the lesion's size or hydrops.

The prognostic value derived from the type of the cystic lung lesion, as described by Stocker *et al.* (type I with cysts >2 cm, type II with cysts <2 cm, and type III without identifiable cysts) [7, 132] or by Adzick *et al.* (microcystic with cysts <5 mm, macrocystic with cysts >5 mm) [7], is the most controversially discussed prenatal parameter (Table 7). Several authors state that solid or microcystic lesions are favorable because of their nature to regress more frequently than lesions with discernible cysts [15, 18, 39, 41, 57, 75, 76, 91, 93, 94, 104, 128]. Conversely, other authors state that a solid or microcystic lesion is a predictor of an unfavorable outcome [4, 7, 21, 79, 107, 137, 138]. The results of my 60-patients-study support the notion that solid appearing lung lesions of Stocker type III and small-cystic Stocker type II lesions are more favorable, attributable to a higher regression rate, than masses with large Stocker type I cysts, which more often increase to critical large mass sizes. A large dominant cyst within the type I lesion is highly critical as it may abruptly increase due to rapid fluid accumulation, as described by Crombleholme *et al.* [34] and also observed in my series. To emphasize again, close ultrasonographic surveillance is required, at least during the critical period of mass size increase, to be prepared for prompt therapeutic interventions in rapidly increasing Type I lesion cases, as mentioned before in CHAPTERS 6.1.2 and 6.1.3.

6.1.5 A major reason for the overestimation of the mortality rate is that the "hidden survival rate" is unaccounted for

The overall mean mortality rate of 22 ± 18.2%, calculated from data published from 1985 to 2007 (Table 6 and Figure 6), is an overestimation of the true mortality rate of fetuses with cystic lung lesions. The earlier performed studies in particular, tended to overestimate the mortality rate, due to a biased selection for the sickest fetuses and attributable to numerous elective termination of pregnancies [7, 107, 138]. As ultrasound techniques have improved, many previously unnoticed lesions with a good prognosis were detected and, as superior pre- and postnatal treatment options have become available, many institutions abandoned the practice of interrupting pregnancies for fetal cystic lung lesions. As a result, from 2003 to 2007, the recent mean mortality rate dropped to 10.9 ± 7.3%. For this calculation I included the data from the fifteen most recent studies of Table 6 and excluded one study with an exceptionally high TOP rate [73]. The mortality rate of 15% in my series lies in between the above-mentioned, overestimated mortality rate of 22% and the more realistic, recent mortality rate of 10.9%. This can be explained by the very long 14-year-period covered in my study, and it reflects the changes toward improved diagnostic and therapeutic techniques at the UCSF Medical Center. In order to account for modern treatment standards, I corrected the individually published mortality rates by calculating a "true mortality rate." To achieve this, I excluded the interrupted pregnancies and the prenatally untreated hydropic fatal cases which otherwise had no other congenital anomalies (Table 6 and Figure 6) from the calculations. The true mean mortality rate dropped to as low as 7.4 ± 6.5%, which is about three times lower than the overestimation.

Another important piece of information that helped with this study – to reflect on the outcome of fetal cystic lung lesions, such as CCAM or BPS – came in fact from the parents of the affected children. There were 22 parents of the 60 study patients who declined to follow the recommendations of their referring doctors to terminate the pregnancy. Their decisions were justified, since their children were later doing fine. In retrospect, these children were considered “miracles of life” by their parents (in communication to me, the conductor of this study). Within this group, only 1 fetus required prenatal surgery and 4 required postnatal surgery due to symptoms. The other 17 children were asymptomatic or had only minor symptoms early after birth. Professor Diana L. Farmer, Professor Ruth B. Goldstein, and I coined the term “hidden survival rate” for this phenomenon. Several other authors also critically reflect on how to counsel parents [64, 91, 101, 104]. The growing number of healthy fetal lung lesion survivors – which were initially given a poor prognosis – made the authors reconsider their parental counseling. McCullagh *et al.* [101] suggest that no specific diagnosis should be given to the parents, instead they should be told that some cystic changes have been observed and further monitoring will be necessary. No action should be taken which might jeopardize the outcome of a benign condition. The fetal treatment specialists of the UCSF Medical Center and the University Hospital Großhadern of the LMU Munich also recommend that physicians adapt to the knowledge of the “hidden survival rate” for fetuses with cystic lung lesions, and that they make proper adjustments in their parental counseling.

6.1.6 The long term outcome is excellent

The long-term outcome of children with prenatally detected cystic lung lesions is excellent, independent ($p>0.3$) of the prenatal outcome predictors, and not influenced by the early (respiratory) outcome as observed in my patients survey. This is backed by the following findings. No fatality occurred past infancy. A single child of this study died in the extended neonatal period, at 2 months of age. In the surveyed literature, only four infant deaths were recorded and all of them occurred within 3 months of birth (Table 6; one case excluded because of uncertain detail).

The initial respiratory difficulties improved in the patients of my study, either in the neonatal period (41%), during the first 2 years (34%), or rarely between 2 and 4 years of age (16%). The majority (75%) was completely asymptomatic at last follow-up, 20% had minor residual labored breathing on exertion or infrequent mild asthmatic symptoms, and only three children who had received operations continued to be moderately symptomatic with limited physical endurance (3 years old), frequent pulmonary infections (5 years old), or asthma (12 years old) (Tables 2.2 and 3). To the best of my knowledge, this report of a comprehensive long-term surveillance of a large cohort of fetuses with cystic lung lesions is unique in the literature. Most of the other published reports focused on perinatal outcome. The few examinations of long-term outcomes were performed on small patient numbers or selected cases (Table 6). So far, only one recent study by Kamata *et al.* [81] presents a comparable long-term study, with a similar follow-up interval (6.9 mean years of Kamata's study versus 5.9 mean years of my study), but with less than one-half as many patients, compared to my study. As I did, Kamata *et al.* also observed that respiratory symptoms, such as frequent respiratory tract infections and

asthmatic attacks, improve or disappear with increasing age. In their series only one 7-year-old child who had massive hydrops during fetal life had persistent severe respiratory restrictions. Two more children are reported by other authors to have pulmonary sequelae and asthma with recurrent pneumonia later in life [103, 128]. All other children with fetal cystic lung lesions who were followed long-term are reported to have complete functional recovery after overcoming the critical neonatal period [23] and are doing well at last follow-up [39, 41, 73, 104]. However, using ventilation and perfusion lung scintigraphy to evaluate the children's lung functions, Kamata *et al.* discovered a significant decrease of lung ventilation and lung perfusion in patients who have had a large fetal mass (low L/T), prenatal hydrops, or required a lobectomy [81]. This suggests that lung scintigraphy appears to be a sensitive method for evaluating even subtle lung function deficits, and it should be applied in future care and research studies of fetuses with lung lesions. In my research, I focused on clinically relevant respiratory symptoms and on the potential interference with the children's or families' daily activities. In this regard, all of the 51 surviving study patients were doing fine except for the three above-mentioned, moderately affected children. Furthermore, prematurity-associated non-respiratory problems, such as prolonged difficulties with feeding, weight gain, and GERD, improved to a milder stage mostly by the age of 2 years. Kamata *et al.* (2006) also observed that failure to thrive is a common complication, but improves with increasing age. They argue that prolonged artificial ventilation, labored respiration, and frequent respiratory tract infections lead to malnutrition, and it may last in patients who have had fetal hydrops, as they experienced with one case [81]. Other major congenital anomalies were seen in 8% (5 of 60) of the patients in my study. This rate is slightly higher than the average anomaly

rate of 5% of the cases included in Table 6. The explanation for this data is that a few studies in Table 6 did not include cases with major anomalies due to the restrictive referral policy of their tertiary care centers or the exclusion of these cases from their research population [34, 46, 47, 59, 143]. Only 3% of the anomalies were detectable before birth in my 60-patients-series. This percentage is comparable with the average frequency of prenatally detected congenital anomalies of about 2% in ordinary pregnancies, observed in the EUROFETUS and EUROCAT study [98]. The incidence of congenital heart diseases is 11.8:1000 (Table 6) and not significantly elevated in fetuses with cystic lung lesions, compared to a general prenatal incidence of 6:1000 to 12:1000 [71]. The computed incidence from the reports summarized in Table 6 is 6.9:1000 for renal agenesis and 2.1:1000 for trisomy 18 in the fetal lung lesion population and it is surprisingly high. This is in contrast to a reported incidence of about 0.3:1000 of each, renal agenesis and trisomy 18, in regular pregnancies [27, 86, 115, 151]. In my 60-patients-series, one unilateral renal agenesis (in association with a Mayer-Rokitansky-Küster-Hauser syndrome) and one ultrasonographically questionable bilateral renal agenesis (not confirmed with an autopsy report) were found, but no cardiac anomalies (only 10 newborns with non-structural, transient cardiac symptoms) or trisomy 18 cases. In summary, the long-term outcome of fetuses with cystic lung lesions, such as CCAM or BPS, is excellent. Most children are postnatally asymptomatic and the other survivors grow out of their initial respiratory symptoms by early childhood at the latest. Only a few exceptional cases remain with prolonged respiratory or non-respiratory anomalies.

There is a significant difference between the long-term outcome of fetuses with CCAM or BPS and the long-term outcome of fetuses with congenital diaphragmatic

hernia (CDH). Neurodevelopmental delay, hearing loss, and growth failure is frequent in children with severe fetal CDH, as recent follow-up studies on CDH show [33, 111]. Mortality and pulmonary hypoplasia rates are much higher in association with prenatally diagnosed CDH than with CCAM and BPS, despite similar ultrasound impressions of the volume of the mass and the compression of the surrounding normal lung during pregnancy [5, 47, 58, 129]. About 30% of CDH patients require ECMO (extracorporeal membrane oxygenation) after birth, and about 25% of the survivors suffer from long-term chronic obstructive airway disease [77, 105]. Only a single child of the 51 survivors in this study of fetuses with cystic lung lesions had ECMO and did not survive. None of the children of this series and of the reported series had long-term neurodevelopmental delays or hearing loss. Only very few children with very large fetal lung masses or hydrops had prolonged respiratory sequelae, as described in CHAPTER 5.2.4 and discussed above in this CHAPTER 6.1.6. The outcome of fetuses with cystic lung lesions is much better than the outcome of fetuses with CDH.

6.2 Management of the patients

6.2.1 Prenatal management recommendations

The ultrasonography provides an important resource for prenatal management. Ultrasonographic screening techniques have become very sensitive in detecting fetal cystic lung lesions. Under rare circumstances where ultrasonographic findings are indistinguishable, fetal MRI can confirm the diagnosis of a lung tumor, determine its origin, and be instrumental in the differentiation from a CDH [22, 74, 120]. Screening for other anomalies, with a particular attention to renal agenesis and trisomy 18, is indicated following the diagnosis of a fetal cystic lung lesion. Serial ultrasound imaging is the method of choice for following the fetuses with lung lesions through pregnancy. Owing to the growth pattern of moderate and large sized lesions, these lesions require closer observation than small sized lesions. During the period of critical mass size increase, between 20 and 28 weeks' gestation, weekly ultrasounds or at least every two weeks are indicated [58]. Small lesions can be followed monthly, as well as stable lesions after 30 weeks' gestation. If the mass enlarges markedly or a dominant cyst within the mass grows rapidly, up to daily ultrasounds are required to rule out fetal ill being, specifically in the event of the development of hydropic symptoms. Alerting mass sizes, indicative for a high risk of hydrops progression, are a CVR of >1.6, an MTR of >0.6, and an L/T of <0.25 [34, 80, 145], as discussed in CHAPTERS 6.1.2 and 6.1.3. Close serial ultrasound surveillance will not miss early signs of a hydrops development, the "point of (almost) no return."

Once hydropic signs emerge, an expeditious decision has to be made in favor of fetal treatment versus delivery. If the fetus is more than 32 weeks of age prompt delivery

is preferred, whereas at less than 32 weeks of age an immediate fetal therapeutic intervention is indicated to have a chance of a successful outcome [34, 58, 152]. Maternal contraindications have to be ruled out prior to the procedure. This strategy is also recommended for other life-threatening fetal tumors, such as giant fetal hepatic hemangiomas, as I pointed out in a previous publication [118]. Even if the fetus is not hydropic, but the lung mass is huge, invasive fetal treatment has to be considered to prevent significant pulmonary hypoplasia. However, no consensus has been reached regarding when and at what size a therapeutic intervention would be advisable for non-hydropic fetuses with huge masses. Fetal treatment options are (serial) aspirations or catheter-induced, thoraco-amniotic shunts for large dominant CCAM type I cysts or for pleural effusion associated with BPS [46, 65, 108]. A more invasive procedure with maternal hysterotomy, fetal thoracotomy, and pulmonary tumor resection is required for fetuses with massive solid appearing cystic lung lesions [65]. The success rate of this procedure is evidently increasing, as discussed in CHAPTER 6.1.3. However, open fetal surgery remains a risky procedure for both the fetus and the mother, and it should be considered only if no other options are available [58]. Further studies on alternative fetal treatment techniques, such as percutaneous radiofrequency ablation for large solid masses [19, 39, 53] and embolization of the aberrant artery for BPS reduction [1, 110, 121], have to prove that these procedures are reliable and safe for the fetus. To treat severe polyhydramnios or solitary massive ascites, minimally invasive procedures such as (serial) amniocentesis [91, 119] or fetal paracentesis [13] can ease these symptoms and may prevent fetal lung growth restriction or prune belly formation. Non-surgical management with medication, such as steroids (via the mother) for tumor reduction [141]

or furosemide and Digoxin (via the umbilical cord) for fetal cardiac failure [9], may also find their way into conventional prenatal treatment. If early delivery is indicated, the fetal treatment specialists of the UCSF Children's Hospital and CHOP [68] recommend the *ex utero* intrapartum treatment (EXIT) for very large lung lesions. With this procedure, the mass is excised at the time of delivery, while the fetus is maintained on placental support. If early postnatal pulmonary hypertension or hypoplasia complicates the recovery of the newborn, transient high-frequency oscillatory ventilation (HFOV) [82, 147], extracorporeal membrane oxygenation (ECMO) [3], or both can be used, in addition to other intensive care treatment options. Institutions where these modern pre-, peri-, and postnatal treatment techniques are established are able to save the lives of severely affected fetuses, and they significantly improve the children's outcomes.

When counseling parents, it is justifiable for physicians to point out the excellent prognosis of fetuses with cystic lung lesions, as coached at the UCSF Medical Center and various other institutions [64, 101, 104]. Although rarely necessary, the need for intense and demanding care during the first few months or at latest up to 3 to 4 years of age has to be addressed. This might be the case when the cystic lung lesion is very large, a fetal hydrops develops, or a fetal therapeutic intervention was performed. Reasons for the intense care are the associated respiratory restrictions and prematurity. Parents of very seriously affected fetuses have to be prepared that although occurring seldom, despite supreme pre- and postnatal treatment, an early pre- or postnatal death cannot be prevented [34, 46, 58, 91, 152]. However, the majority of fetuses with cystic lung lesions is doing fine, and parents of these fetuses do not need to be counseled about the worst-case scenario.

6.2.2 Postnatal management recommendations

As most institutions with ample experience in postnatal management of children with congenital cystic lung lesions, the specialists at the UCSF Children's Hospital recommend postnatal radiological examinations. An initial x-ray is indicated immediately after birth, even if the newborn is asymptomatic. If the initial x-ray is negative, the child needs a subsequent computed tomography (CT) at the age of 1 month. Many lesions are identified on postnatal CT, even if they disappear on prenatal ultrasound or are not demonstrable on postnatal x-ray. Fetal cystic lung lesions often decrease before birth, but they rarely dissolve completely [15, 39, 43, 94, 100, 129, 144]. Of the 7 lesions that disappeared on prenatal ultrasound, in my 60-patients-series, 3 were demonstrated on postnatal CT. The others had no CT or MRI done, including two with negative x-rays. A postnatal magnetic resonance imaging (MRI) is a radiation-free alternative to a CT scan in respiratory stable patients, but it reveals less information about the pulmonary parenchyma than a CT [23, 87, 133, 147]. However, the pre-operative demonstration of the supplying and draining vessels to a bronchopulmonary sequestration with an MRI scan, using a three-dimensional, contrast-enhanced MR angiography, may be superior to an enhanced CT and more practical than an invasive digital subtraction angiography (DSA) [42, 85, 96, 153]. The postnatal imaging studies are obligatory for further therapeutic proceedings.

No controversy exists about the surgical proceeding in symptomatic patients. Immediate, urgent resection of the cystic lung lesion is mandatory if the neonate becomes symptomatic. The prenatal diagnosis is helpful in recognizing neonates at high risk of postnatal respiratory distress, and it enables programmed and immediate surgical

treatment [21, 107, 136], if necessary. Children who are becoming symptomatic later in life are also advised to have the cystic lung lesion excised. However, the prenatal detection and the postnatal radiological confirmation of asymptomatic cystic lung lesions have ignited a discussion about the removal of asymptomatic lesions, in particular about the timing of the removal. Most pediatric surgeons advocate elective tumor resection. At the UCSF Medical Center and at many other institutions, pediatric surgeons recommend early elective resection of radiologically confirmed lesions, usually after 1 month of age [34, 58, 131, 147] (Table 6). At this age the child has adapted to the postnatal circulation and anesthetic risks are reduced. Other surgeons suggest an elective resection of prenatally detected lung tumors at 2 to 3 months [21, 83], between 3 and 6 months [26], or between 6 and 18 months of age [23, 48, 133, 140]. In the most recent clinical study on the management and outcome of fetal CCAMs, published while proofreading this paragraph, the authors suggest an early postnatal thorax CT and the operation of all CT-confirmed cases – already before the newborn's discharge from the hospital. This recommendation comes in view of the significant risk of serious early infective complications in non-operated babies, compared to the relatively low postoperative morbidity in operated babies [29]. Postoperative lung growth after decompression, predominantly during the first 2 years of life, considerably compensates the loss of resected lung tissue [47, 54, 129, 139]. The minimal risks associated with the surgery and the benefit of eliminating the need for life-long surveillance by eliminating the ongoing risk of potential pulmonary infections, pneumothoraxes, and bleeding from an anomalous artery (supplying a BPS or CCAM-BPS-hybrid) justify the elective resection of asymptomatic congenital cystic lung lesions [13, 15, 34, 39, 75, 92, 103, 131, 140, 147].

Further, a malignant transformation of a remaining CCAM or CCAM-BPS-hybrid into bronchoalveolar carcinoma, pleuropulmonary blastoma, or pulmonary rhabdomyosarcoma, even though rare, is an ongoing threat to the patient and justifies prophylactic operation [3, 14, 37, 45, 52, 61, 67, 106, 113, 114, 123, 134, 142]. An experienced pediatric surgeon can safely – and with postoperative minimal morbidity – perform a thoracotomy with a segmentectomy or a lobectomy in infants. However, a few complications after thoracotomy are reported, such as prominent scarring and musculoskeletal deformities. Such reports lead to recommendations against elective surgery [10, 144, 146]. Bunduki *et al.* even report a case of death in an electively operated 2-months-old infant with fetal CCAM [21]. In contrast to this case report, Ierullo *et al.* report another case of death in a neonate with asymptomatic CCAM, which was not operated [75]. Both died from the same complication, which was sepsis. The experiences with post-thoracotomy complications in my follow-up study were that 8 children had developed a prominent thoracic scar, a pectus excavatum, or both. All of these children were operated prior to the age of 1 month, including three fetal surgery cases. One of these fetal surgery cases, in addition to the thoracic scar deformations, developed a significant residual CCAM (the only late residual in this series: case no. 55) and had a revision of the residual, the scar, and the pectus at the age of 3 ½ years. The management of this case and the implications of residual CCAMs and thoracic scar deformations after fetal surgery are discussed in detail in our 2006 published case report of PART II of this doctoral thesis. Some pediatricians propose that delaying surgery into childhood may reduce chest deformities and somatic growth impairment [11, 73, 117]. This therapeutic approach is not supported by the UCSF pediatric surgeons. Failure to

thrive was significantly associated with prematurity, not with the age at surgery, as the results of my long-term follow-up study show. Prematurity though, was found more often in severely affected children, who were candidates for an early operation. Other than that, children with delayed operations, after becoming symptomatic later in life, had prolonged hospital stays compared to the early-operated patients, as described in CHAPTER 5.2.6. Moreover, new minimally invasive surgical techniques are increasingly available, which further minimize postoperative complications. Thoracoscopic lobectomy (with or without video assistance) has become a feasible and safe procedure in very small patients, with an excellent cosmetic result [8, 16, 31, 38, 40, 78, 84, 126, 135, 148]. Five thoracoscopic postnatal operations (four elective and one for symptoms) were performed on the patients of my study series, carried out by Professor Craig T. Albanese. All of them were uncomplicated and showed an excellent cosmetic outcome. Another minimally invasive, new technique is the transcatheter arterial embolization (TAE) of bronchopulmonary sequestrations. Recent studies demonstrate that it is safe and effective [1, 13, 35, 95], though follow-up studies have to be developed in order to show that the regressions after embolizations last. The early postnatal surgery, from the perspective of a risk/benefit analysis, is justified, even in asymptomatic patients. Resecting the lung tumor eliminates the need for a lifelong surveillance with radiation exposure and the ongoing risk of tumor-related complications. This outweighs the small risk of postoperative morbidity. A definite removal of the lung mass also reduces parental anxiety. In addition, minimally invasive surgery further minimizes postoperative morbidity. This should be considered when counseling future patients.

In conclusion, early respiratory symptoms can be predicted using prenatal mass size measurements. The fetus requires close ultrasonographic surveillance, at least during the period of critical mass size increase. Early signs of a hydrops justify prenatal therapy. Timely pre- or postnatal therapeutic interventions reduce mortality and morbidity of children with symptomatic lung masses. Most of the early respiratory and non-respiratory symptoms resolve in the neonatal period or until the age of 2 years, and the long-term outcomes are excellent.

TEIL II

Residuum einer kongenitalen zystisch-adenomatoiden Malformation der Lunge mit starker Narbenbildung und Deformation der Brustwand nach fetaler Chirurgie: Ein Fallbericht [116]

PART II

Residual congenital cystic adenomatoid malformation and thoracic scar deformation after fetal surgery: a case report [116]

1. Zusammenfassung Teil II

Pränatale Behandlungsmethoden für Feten mit kongenitalen zystisch-adenomatoiden Malformationen der Lunge („congenital cystic adenomatoid malformation of the lung“, CCAM) richten sich nach dem Schweregrad der Krankheit und dem Gestationsalter. Feten, die vor Vollendung der 32. Schwangerschaftswoche (SSW) einen Hydrops entwickeln, sind Kandidaten für eine *in utero* Therapie. Die fetale CCAM Resektion ist eine der Therapiemöglichkeiten und sollte durchgeführt werden bevor der fetale Hydrops ein fortgeschrittenes Stadium erreicht. Postoperative Spätkomplikationen sind selten und, ebenso, wenig untersucht. Wir berichten über ein 4-jähriges Mädchen, das im Rahmen der Forschungsarbeiten von TEIL I (Fallnummer 55) nachuntersucht worden war. Nach einer fetalen CCAM Resektion in fortgeschrittenem Hydropsstadium traten bei diesem Kind ein CCAM-Residuum und eine deformierende Thoraxnarbenbildung auf. Ziel dieser Anschlussstudie TEIL II war es, diejenigen Einflussgrößen zu bestimmen, die auf post-fetalchirurgische Spätkomplikationen einwirken. Deshalb verglichen wir diesen Fall mit acht weiteren Fällen unserer Institution (darunter vier Fälle aus der Studie TEIL I mit den Fallnummern 51-54), in denen eine fetalchirurgische CCAM Resektion durchgeführt worden war und die Kinder überlebt hatten.

Im folgenden Fallbericht befassen wir uns ausführlich mit dem Fetus (Fallnummer 55 aus der Studie TEIL I), bei dem mit 18+2 SSW eine rechtsseitige CCAM-Läsion im pränatalen Ultraschallbild festgestellt wurde. Der Tumor vergrößerte sich rasch, und innerhalb einer Woche entwickelte sich ein schwerer fetaler Hydrops. Die Abklärungen, die an unserer Institution in der 21. SSW durchgeführt wurden, ergaben

einen überdimensional großen und überwiegend soliden CCAM-Tumor. Dieser verursachte eine ausgeprägte, linksgerichtete Mediastinalverschiebung und einen enormen fetalen Hydrops, der aus erheblichem Aszites, Pleuraergüssen und einem Skalpödem bestand. Es wurden keine weiteren morphologischen Anomalien beobachtet. Der Fetus wurde mit 20+3 SSW operiert. Zwischen der rechten 6. und 7. Rippe wurde thorakotomiert. Der Lungentumor, der den gesamten rechten Unter- und Mittellappen vereinnahmte, wurde vom rechten oberen Lungenlappen freipräpariert und mit zwei elektrischen Schlingen („Endoloops“) vom Lungenhilus abgesetzt. Die fetale Brustwand wurde mit einer fortlaufenden Allschichtennaht wieder verschlossen. Histologische Untersuchungen der Tumormasse bestätigten die Diagnose einer mikrozystischen CCAM. Der fetale Hydrops bildete sich drei Wochen nach der Operation wieder zurück. Vorzeitiger Blasensprung und Chorioamnionitis erzwangen die Geburt eines 29+5 SSW alten und 1500 Gramm schweren, weiblichen Kindes durch einen Kaiserschnitt. Nach der Geburt war ein verlängerter Krankenhausaufenthalt von 99 Tagen aufgrund von Frühgeburtlichkeit, erhöhtem Sauerstoffbedarf und chronischer Lungenkrankheit erforderlich. Die Symptome hielten auch nach Krankenhausentlassung weiter an. Ein CCAM-Residuum war weder auf den fetalen Ultraschallbildern, am ersten postoperativen Tag nach der Fetalchirurgie, noch im Thorax-Computertomogramm (CT), einen Monat nach der Geburt, zu sehen; während eine postoperative Vernarbung der Lunge anhand der CT-Bilder wahrscheinlich zu sein schien. Ein späteres Thorax-CT, im Alter von 3 ¼ Jahren, zeigte unveränderte Abnormalitäten im rechten unteren Hemithorax. Diese Abnormalitäten wurden nun als post-fetalchirurgische Veränderungen oder als CCAM-Residuum der rechten Lunge interpretiert. Die bereits bei der Geburt des Kindes

festgestellte, starke Narbenbildung und Deformation der rechten Brustwand wurde im Laufe der Zeit immer auffälliger – wegen der wulstigen und furchigen Hautveränderungen, der Fusionierung mehrerer Rippen und aufgrund des Muskeldefektes der lateralen Brustwand. Hinzu kam, dass der Muskeldefekt zu einer Bewegungseinschränkung des rechten Armes und der Schulter führte. Im Alter von 3 ½ Jahren wurde eine zweite, revidierende Operation durchgeführt. Das CCAM-Residuum wurde reseziert, wonach es zu einer raschen Wiederauffüllung des Brustkorbes durch gesundes Lungengewebe aus dem zurückgebliebenen rechten Oberlappen kam. In derselben Operation wurde auch eine Rekonstruktion der Brustwand durchgeführt. Hierbei wurde das dichte Narbengewebe entfernt, die fusionierten Rippen voneinander getrennt und der Muskel, der sich unterhalb der Narbe zurückgezogen hatte, zurück verlagert. Die Atembeschwerden besserten sich nach der Operation dramatisch, und das kosmetische Resultat war gut. Wir verglichen diesen Fall mit acht weiteren Überlebenden nach fetaler CCAM Resektion von unserer Institution, welche jedoch keine späten post-fetalchirurgischen Komplikationen entwickelt hatten. Im Unterschied zu den anderen Überlebenden war in diesem Fallbeispiel der Tumor überdimensional groß und wuchs außergewöhnlich schnell. Ein sich rasch verschlechternder Hydrops trat mit 19+3 SSW auf, also früher als in allen anderen Fällen.

Fazit der Studie ist, dass eine pränatale Behandlung von Feten mit CCAM und Hydrops lebensrettend ist und eine Herausforderung für den Chirurgen darstellt. Eine fetaltherapeutische Operation sollte nicht zu spät erfolgen. In diesem Fall wurde ein Fetus mit einem äußerst schnell wachsenden und überdimensional großen CCAM-Tumor, in weit fortgeschrittenem Hydropsstadium, erfolgreich vor der Geburt operiert. Dennoch

traten im postoperativen Verlauf Komplikationen auf, nämlich eine chronische Lungenkrankheit und eine kosmetisch unbefriedigende Brustwanddeformation mit starker Narbenbildung. Die Faktoren, die zur Beeinträchtigung der Wundheilung nach fetalchirurgischen Eingriffen führen, sind sowohl (i) ein ungünstiger Allgemeinzustand des Feten (wie das Stadium der kardiovaskulären Dekompensation bei einem Hydrops), als auch (ii) ein ungünstiger Zustand der Operationswunde aufgrund von Hautödemen, die die Gewebeperfusion behindern und die Entzündungsreaktion verlängern, und ebenso (iii) eine unvorteilhafte chirurgische Nahttechnik. Auch die Dekompression der Brusthöhle, die der operativen Entfernung eines sehr großen Lungentumors folgt, mag zur Entwicklung einer postoperativen Brustwanddeformierung beitragen. Ein CCAM-Residuum ist eine seltene Komplikation nach pränataler oder postnataler Tumorresektion. Unser Fall zeigt auf, dass ein CCAM-Residuum höchstwahrscheinlich mit einer beschleunigten Resektionstechnik bei Notfalleingriffen zusammenhängt, die bei schwer kranken, hydropischen Feten und Neugeborenen angewendet wird, um die Operationszeit zu verkürzen. Wird ein Kind nach einer CCAM Resektion mit chronischen Atembeschwerden auffällig, so sollte an ein postoperatives Residuum gedacht werden. Die Unterscheidung zwischen einem CCAM-Residuum und einer postoperativen Narbenbildung in der Lunge kann schwierig sein. Deshalb empfehlen wir bei persistierenden postoperativen respiratorischen Symptomen eine Thorax-CT-Aufnahme, mit oder ohne (serielle) Thorax-Röntgenaufnahmen, während der ersten 6 bis 12 Lebensmonate, unter Umständen auch noch später. Eine chirurgische Revision der späten post-fetalchirurgischen Anomalitäten ist bei stark symptomatischen Kindern indiziert und hat gute Erfolgsaussichten.

2. Summary Part II

Prenatal management of fetuses with congenital cystic adenomatoid malformations of the lung (CCAM) depends on the severity of the disease and the gestational age. Fetuses developing a hydrops prior to the age of 32 gestational weeks are candidates for in *utero* treatment. Fetal CCAM resection is one of the treatment options and should be performed before the hydrops becomes advanced. Late postoperative complications are rare and likewise not well studied. We report a case of a 4-year-old girl, who had a follow-up in the course of the study PART I (case number 55). The child developed a residual CCAM and a deforming thoracic scar after prenatal CCAM resection for advanced hydrops. The purpose of this successional study PART II was to identify the factors related to late post- fetal surgery complications. Thus, we compared this case with eight other fetal CCAM resection survivors of our institution (among these were four cases of the study PART I with the case numbers 51-54).

The following detailed case report is about the fetus (case number 55 of the study PART I) that had a right-sided CCAM detected on prenatal ultrasound at 18.3 weeks' gestation. The lesion was rapidly growing, and severe fetal hydrops developed over 1 week. The investigations at our institution at 20 weeks gestation revealed a huge, predominantly solid CCAM, which caused marked leftward mediastinal shift and tremendous hydrops as evidenced by a large ascites, pleural effusion, and scalp edema. No other morphological abnormalities were identified. The fetus underwent an operation at 20.4 weeks of gestation. A right thoracotomy between the 6th and 7th rib was performed. The lung mass, which occupied the entire right lower and middle lobe, was dissected off the right upper lobe and amputated from the pulmonary hilum with two

Endoloops. The fetal chest wall was closed with running all-layer sutures. The histologic examination of the mass confirmed the diagnosis of a microcystic CCAM. The hydrops resolved three postoperative weeks later. Premature rupture of the membranes and chorioamnionitis mandated the delivery of a 1500-g female via caesarean section at 29.7 weeks gestation. A prolonged hospital stay of 99 days after birth was required due to prematurity, oxygen requirement, and chronic lung disease. The symptoms were ongoing after discharge from the hospital. A residual CCAM lesion was not seen on fetal ultrasound on postoperative day 1 after fetal surgery, nor on chest computed tomography (CT) scan at 1 month of age; though, postoperative scarring of the lung was suggested after the CT. A subsequent CT scan of the chest, at 3 ¼ years of age, still showed an abnormality in the right lower hemithorax. This abnormality was then interpreted as post-fetal surgery changes or residual CCAM in the right lung. The child's chest wall deformity and the prominent right thoracic scar, already diagnosed following birth, became more and more prominent – with bulging and indented skin, with several ribs fused together, and with a muscle defect at the lateral chest wall causing some limitation of the right arm and shoulder movements. A second, revising operation was done at 3 ½ years of age. The residual CCAM was resected allowing the remaining intact right upper lobe to quickly refill the chest. In the same operation, a chest wall reconstruction was performed by resecting the dense scar, separating the fused ribs, and repositioning the retracted muscle underneath the scar. Postoperatively, the respiratory symptoms improved dramatically together with a good cosmetic result. We compared this case with eight other fetal CCAM resection survivors of our institution, which had not developed late post-surgery morbidity. Different from the other survivors, this case had an

extraordinary huge and rapidly growing mass. An expeditiously progressing hydrops developed at 19.4 weeks' gestation, and this was earlier than in all other cases.

In conclusion, the prenatal management of fetal CCAM with hydrops is crucial and challenging for surgeons. Fetal surgery should not be delayed. Our case of a fetus with a rapidly growing, huge CCAM and advanced hydrops was successfully operated before birth. However, chronic lung disease and a cosmetically unsatisfying chest wall deformity with a prominent thoracic scar complicated the postoperative course. The factors contributing to impaired wound healing after fetal surgery are (i) an unfavorable underlying condition of the fetus (such as a state of cardiovascular decompensation under hydrops condition), as well as (ii) an unfavorable condition of the surgical wound due to skin edema compromising tissue perfusion and prolonging the inflammatory response, and also (iii) a disadvantageous suturing technique. Surgical decompression of the thoracic space after removal of a huge lung tumor may also contribute to the development of a postoperative chest wall deformity. A residual CCAM is a rare complication after prenatal or postnatal tumor resection. As our case demonstrates, a residual CCAM is most likely associated with an accelerated resection technique – performed to shorten the operation time and necessary for emergency procedures in very sick hydropic fetuses or neonates. A postoperative residual CCAM should be suspected in a child presenting with chronic respiratory symptoms. The differentiation between a residual CCAM and postoperative intrapulmonary scarring might be difficult. In the case of enduring postoperative respiratory symptoms we recommend a chest CT scan, with or without (serial) chest x-rays, during the first 6 to 12 months of life or even longer. A surgical

revision of a late post- fetal surgery aberration is indicated in significantly symptomatic children and has a good chance of success.

3. Introduction

Congenital cystic adenomatoid malformation (CCAM) is an abnormality in lung development that is characterized by an overgrowth of terminal bronchioles and a lack of normal alveoli [28, 132]. The clinical course of CCAM is variable [5, 39, 119, 144]; therefore, prenatal management depends upon the severity of disease and gestational age. Expectant management is recommended if the size of the lesion is small and there are no signs of hydrops [5]. Once hydrops occurs, spontaneous resolution is extremely rare [50, 60, 69]. At that point fetuses are at high risk for demise [5, 6, 46]; thus, careful management is important. Early delivery to resect the lesion either postnatally or intrapartum using the *ex utero* intrapartum treatment (EXIT) strategy [70] are options for hydropic fetuses greater than 32 weeks of gestation, whereas previable cases are candidates for in utero treatment [5]. Fetal CCAM resection is considered if thoracentesis or thoraco-amniotic shunt for large cysts is not possible or has been unsuccessful [6]. More recently than this case, maternal steroids treatment has been associated with resolution of hydrops in some cases [141].

Timing of prenatal CCAM resection is crucial for a favorable outcome. Fetal surgery is only indicated after hydrops develops. On the other hand, performing the operation once hydrops is far advanced may be too late to rescue the fetuses [6]. Herein, we report a case of prenatal CCAM resection in a fetus with advanced hydrops, who survived and is doing well at long-term follow-up 4* years later (*corrected). However, the child had a difficult early postnatal course with postoperative complications owing to residual CCAM and deforming thoracic scar.

4. Case

A 44-year-old white woman (gravida 6, para 1) was referred from Oregon to the University of California, San Francisco Fetal Treatment Center at 20 weeks of gestation for evaluation of a right-sided CCAM in her fetus. The lesion was initially detected on routine ultrasound (US) at 18 weeks of gestation and was growing rapidly. Severe hydrops had developed over 1 week.

Transabdominal US performed at our institution at 20 weeks of gestation revealed a huge right-sided CCAM that was predominantly solid with several small cysts. The mass extended across the midline and caused marked leftward mediastinal shift as well as mass effect on the right diaphragm. The fetus had tremendous hydrops as evidenced by large ascites, pleural effusion, and scalp edema. There was mild polyhydramnios. Fetal echocardiogram demonstrated a small heart with good function, and no other morphological abnormalities were detected; fetal karyotype was normal.

After extensive discussion with the Fetal Treatment Center team regarding fetal prognosis and the risks and benefits of fetal treatment, the parents decided to undergo fetal surgery.

The fetus underwent operation at 20 3/7 weeks of gestation. After maternal laparotomy, the placental and fetal positions were localized, and a uterine incision was made. A right thoracotomy incision was performed between the sixth and seventh rib, and the right lung mass immediately "popped" from the fetal chest. The right upper lobe was dissected off, and the inferior pulmonary ligament was taken down with electrocautery. Two 0-chromic Endoloops were placed around the hilum of CCAM, and the mass was then amputated. The fetal chest wall was closed with 4-0 Maxon running

all-layer suture. Antibiotic and warm saline were instilled into uterine cavity once the hysterotomy was closed. Both mother and fetus tolerated the procedure well. Histologic examination of the mass confirmed the diagnosis of microcystic CCAM.

On postoperative day 1, no remaining CCAM lesion was seen on US. Hydrops was still present at that time but resolved 3 weeks later, with resolution confirmed by repeated US. Mother returned to Portland, Ore, and the pregnancy continued uneventfully until 28 weeks of gestation when premature rupture of the membranes occurred. Chorioamnionitis mandated the delivery at 30 weeks, and a 1500-g female neonate was delivered via caesarean section with Apgar scores of 6, 6, and 7, at 1, 5, and 10 minutes, respectively.

A prominent right-sided scar with deformation of the underlying ribs was found on the infant's right chest wall. The newborn developed mild respiratory distress syndrome, requiring ventilation for 2 days. Prematurity, oxygen requirement, and chronic lung disease required the infant to stay in the hospital for 99 days. Chest computed tomographic (CT) scan at 1 month suggested postoperative scarring of the lung in the right lower hemithorax, but a residual CCAM could not be excluded.

The infant had ongoing symptoms of chronic lung disease after discharge from the hospital. Her right thoracic scar became more prominent with bulging and indented skin. Several ribs fused together, and there was a muscle defect in the lateral chest wall (Figure A). Until 3 years of age, the child had some limitation of right arm and shoulder movement. A CT scan of the chest at 3 ¼ years of age still showed an abnormality in the right lower hemithorax, which was interpreted as postfetal surgery changes or residual CCAM of right lung. At that point, the parents were counseled about possible

reexploration for residual CCAM of the remaining right lung and simultaneous chest wall reconstruction to correct the bony and muscular chest wall deformity.

The second operation was done at 3 ½ years of age. At exploration, there was dense scar over the fused ribs, and the muscle underneath the scar was found to have retracted completely away from the fused ribs contributing significantly to the chest wall deformity. The scar was resected and the ribs separated. There was residual CCAM in the same residual tissue from the right lower lobe or middle lobe. The right upper lobe was intact and free of CCAM, and quickly filled the chest after resection of the residual CCAM.

The chest wall deformity and the respiratory symptoms improved dramatically. The child's chest is symmetrical and the scar is very thin (Figure B).

Figure A. Right thoracic scar deformation at 3 years of age.

Figure B. The child's chest at 9 months after surgery showed little remaining indentation and thin scar.

Finally, under institutional review board approval, we reviewed CCAM cases with hydrops evaluated at our institution from 1990 to 2004 to identify potential factors related to postfetal surgery complications; the results are summarized in Table A. Of 18 cases with complete data, there were 9 cases including the patient reported in this article who survived after fetal surgery. With the exception of the present case, no other infants had postsurgery morbidity. The only factor that distinguished this one case that developed a complication was that this fetus developed hydrops earlier than others (19.4 vs 24.9; range, 22.4 - 27.6 weeks of gestation). The early development of hydrops, the microscopic type and large size of the lesion, and the need for rapid resection and chest wall closure probably all contributed to developing the postoperative chest wall deformity and residual CCAM.

Table A. Cystic adenomatoid malformation cases with hydrops who survived after undergoing fetal surgery in our institution from 1990 to 2004

Case no.	CCAM type	Severity of hydrops	Poly-hydramnios	Other prenatal treatment	Type of surgery	GA at hydrops diagnosis	GA at surgery	GA at delivery	Postsurgery complication
1	Macrocystic	A, E, P	Yes	Thoraco-amniotic shunt	LLL	24,7	25,7	34,4	No
2	Macrocystic	A, E	No	No	LLL	23,1	23,4	30,7	No
3	Macrocystic	A, E	Yes	No	LLL	26,9	27,1	27,7	No
4	Macrocystic	A, E	Yes	No	LUL	27,6	27,7	34,1	No
5	Macrocystic	A, E	No	No	LLL	25,6	25,9	33,3	No
6	Macrocystic	A, E	No	Thoracentesis	RML	23,3	24,3	25,9	No
7	Macrocystic	A, E	Yes	Thoracentesis	RML, RLL	25,6	25,9	33,9	No
8	Microcystic	A	Yes	No	RP	22,4	22,7	32,9	No
9[a]	Microcystic	A, E, P	Yes	No	RML, RLL	19,4	20,4	29,7	Residual CCAM, thoracic scar

All cases had mediastinal shift. GA indicates gestational age; A, ascites; E, subcutaneous edema; P, pleural effusion; LLL, left lower lobectomy; LUL, left upper lobectomy; RML, right middle lobectomy; RLL, right lower lobectomy; RP, right pneumonectomy.
[a] Current case.

5. Discussion

Intrauterine therapy is a proven option for treatment of fetal CCAM. Thoracentesis [112] or thoraco-amniotic shunt [30] is performed in macrocystic lesions only, whereas surgical resection can be done in both macrocystic and microcystic types [6]. Although prenatal resection of CCAM has been performed for many years, standard criteria in selecting eligible cases has not been established.

Currently, fetal surgery for CCAM is recommended in those fetuses who develop hydrops before 32 weeks of gestation. Although resolution of hydrops is extremely rare, it has been reported either with [10, 30, 49, 112] or without [50, 60, 69] medical therapy. Therefore, performing the operation in hydropic cases late in gestation (later than 28 weeks) may be unwarranted. However, if hydrops does progress rapidly in a short period, then surgery should not be delayed. Adzick et al [5] reported that hydropic fetuses who underwent in utero resection of CCAM had a mortality rate of 38%; one cause of fetal death was delayed surgery. We have had similar experiences. As a result, prenatal management for CCAM with hydrops is crucial and challenging. In the case presented in our article, hydrops developed early (19 weeks of gestation) and progressed rapidly. The fetus was critically ill at the time of operation, but the hydrops resolved and the fetus survived to delivery at 30 weeks. Unexpectedly, residual CCAM and thoracic scar complicated the postoperative course.

One concern in performing open fetal surgical intervention is the healing process itself. The healing response of skin and muscle are dependent on both underlying condition and the wound [150]. In this case, factors contributed to impaired healing, including hydrops and skin edema, which can compromise tissue perfusion and lead to a

prolonged inflammatory response to wounding [150]. In addition, in this case, the fetus was in heart failure and unable to tolerate a prolonged operation. Thus, operative time was shortened by closing the fetal chest very rapidly with all-layer suture. We postulate that both tissue edema and suturing technique contributed to abnormal healing that resulted in chest wall deformity. Another factor that may have contributed to the chest wall deformity is the surgical decompression of the thoracic space from removal of such a large tumor.

Residual CCAM is a rare complication after resection of the mass. In a review of the literature from 1980 to 2004, only 1 case of residual CCAM after segmentectomy in early neonatal period was reported [128]. In elective operations after birth, it is not difficult to define whether the residual parenchyma of the lobe surrounding the affected segment is normal or abnormal [150]. However, in an emergency procedure performed very rapidly (20 minutes) in such a sick 500-g, 20-week fetus, some residual CCAM from the huge microcystic mass is left surrounding the pulmonary vessels at the root of the resected lobe.

Because residual CCAM can occur after fetal lobectomy, we recommend that, even if a lesion cannot be seen on postoperative US, the neonate should be followed up closely with serial chest radiographs and/or CT scans during the first 6 to 12 months of life. The length of follow-up will depend on the presence or absence of signs and symptoms of respiratory disease. In this case, serial chest x-rays and CT scans showed an abnormality in the right lower hemithorax. However, it was difficult to differentiate between postoperative scarring and residual CCAM of right lower lung until the child was 3 years old, when we thought the risk of reoperation was outweighed by the

significant respiration problems including recurrent pneumonia. We suggest that residual CCAM should be suspected when an infant has chronic respiratory symptoms, along with abnormal serial chest radiographs or CT scans.

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APPENDIX

(16 pages)

1.1 Parents recruitment letter

(2 pages)

1.2 Parents questionnaire

(4 pages)

1.3 Parents telephone script

(2 pages)

2.1 First Committee on Human Research (CHR) approval letter

(1 page)

2.2 Second CHR approval letter

(1 page)

2.3 Cover letter of the annual renewal of the subcommittee reviewed research study

(3 pages)

2.4 Research protocol of the annual renewal of the subcommittee reviewed research study

(3 pages)

UCSF FETAL TREATMENT CENTER

513 PARNASSUS AVENUE,
ROOM 1601 HSW
SAN FRANCISCO,
CA 94143-0570

OFFICE: 1-800-RX-FETUS
FAX: (415) 476-2314
WEB: fetus@USHC.org

«Date»

Dear «Last_Name» family

We are writing to ask for your help with a survey being conducted by the Fetal Treatment Center of the University of California, San Francisco (UCSF). Doctors Diana Farmer and Ruth Goldstein and medical student Eva Bartsch are conducting this survey to find out how children who were diagnosed before birth with Congenital Cystic Adenomatoid Malformation of the Lung (CCAM) or Pulmonary Sequestration (PS) are doing later in life. The knowledge we gain from this study will help us counsel parents in the same situation that confronted you when you were referred to our Fetal Treatment Center during pregnancy.

Your participation in this study is very important for us. If your child has not survived, we first want to express our deepest sympathy and we would be especially grateful for your participation. Please follow the same instructions explained in the next paragraph as for parents whose children survived.

If you choose to participate in this study, we would like you to (a) complete the enclosed Questionnaire about your child, and (b) to choose one of the four options on the Acceptance & Refusal Card most appropriate to you. It will take approximately 10-15 minutes to answer the questions and to provide us with your doctors' addresses and phone numbers. Please return the completed Questionnaire and the checked Acceptance & Refusal Card to us in the pre-addressed and stamped envelope. After receiving your papers by mail, we will assume that we have your permission to (a) review your child's medical records and (b) to call your doctors with some additional questions. If we do not hear back from you within three weeks, we will contact you and perform the same survey over the phone.

Participation in research involves some loss of privacy; however, your records will be handled confidentially. Only Dr. Farmer, Dr. Goldstein and Ms. Bartsch will temporarily have access to your sensitive data. There will be NO costs to you as a result of taking part in this study.

If you have any questions please do not hesitate to contact us. You are very welcome to call us on our study phone at (510) 681-8160 during business hours or leave a message after hours. You can also send an e-mail to us at bartsch@itsa.ucsf.edu or Ruth.Goldstein@radiology.ucsf.edu . If for some reason you do not wish to contact the research doctors, you may contact the Committee on Human Research, which is concerned with the protection of volunteers in research projects. You may reach the committee office between 8:00 and 5:00, Monday through Friday, by calling (415) 476-1814, or by writing: Committee on Human Research, Box 0962, University of California, San Francisco, San Francisco, CA 94143.

«random»

PARTICIPATION IN RESEARCH IS VOLUNTARY. You are free to decline to be in this study. Please indicate this on the Acceptance & Refusal Card. Your decision as to whether or not to participate in this study will have no influence on your present or future care.

If you agree to participate in this study please return the filled-out Questionnaire and the checked Acceptance & Refusal Card to us in the pre-addressed and stamped envelope.

We apologize for any inconveniences related to this study. If you are a parent whose child passed away, we want to express again our deepest sympathy to you.

Thank you very much for your time and cooperation.

Sincerely,

Diana Farmer, MD
Associate Professor of Surgery, Pediatrics
and Obstetrics & Gynecology
Fetal Treatment Center
University of California, San Francisco

Ruth Goldstein, MD
Professor of Radiology
and Obstetrics & Gynecology
Fetal Treatment Center
University of California, San Francisco

Eva Bartsch, Medical Student
Fetal Treatment Center
University of California, San Francisco

UCSF FETAL TREATMENT CENTER - PARENT QUESTIONNAIRE

«random»

INSTRUCTIONS: This questionnaire is intended for parents whose child has had a lung mass (CCAM or PS) detected before birth. Both parents whose child survived and those unfortunate parents whose child has passed away may complete the questionnaire. If your child has passed away please answer the questions with regard to the health of your child before he/she died. Please provide us with the name, city & state, and phone number of the hospitals and doctors involved in your child's care (see question 5 and 14). If care was provided at UCSF Medical Center you may simply write "UCSF". All of the information you provide will be held in strict confidence.

Please return the filled-out Questionnaire and the checked Acceptance&Refusal-Card to us in the pre-addressed and stamped envelope provided. Thank you very much.

Question 1a

When was your child born? ……..……...……...……..……

(date of birth)

Question 1b

Did your child pass away?

☐ NO

☐ YES **:**

a) How old was your child when he/she passed away? ….……..……..…

(age at death / and date of death)

b) Cause of death? ……...……...……...…..……..…

c) Was an autopsy performed? ……...……...……...……...……...…

(hospital's name, city & state, and phone number / do you permit us to receive the medical records?)

Question 2

What is your child's gender?

❑ girl

❑ boy

Question 3

How big is your child today?

a) Weight (pounds) : ……..……..

b) Height (inches) : ……..……

Question 4

Did your child have lung surgery?

☐ NO

☐ YES **:**

a) How old was your child when he/she had lung surgery? ……..…..……..……

(age / date / several times? / also before birth ?)

b) Why did your child have lung surgery?

- ❑ trouble breathing
- ❑ infections of the lung (pneumonia, bronchitis, recurrent or chronic cough)
- ❑ to prevent future problems
- ❑ other: ……..…...…....

c) After lung surgery your child's health was **:**

- ❑ better
- ❑ same
- ❑ worse (please explain): ……..……

d) Do you know the type of lung surgery performed? ……..…...……..……..……

(resection? / location & side / extension & size)

e) At which hospital was the lung surgery done? ……..…...……..……

(hospital's name, city & state)

Question 5

Which of the following Imaging Studies has your child had?

BEFORE BIRTH:	**When?** (at which age(s) ? / how many times?)	**Results?** (no problem?/ lung abnormality?/ mass increased or decreased?/ residual?)	**Hospital or Doctor?** (at which hospital or doctor's office was the image done: Name, City & State and Phone)
prenatal Ultrasounds (beside UCSF- ultrasounds?)			
AFTER BIRTH:			)
Lung-X-Rays			
CT scans (Computer Tomography)			
MRI (Magnetic Resonance Image)			
Pulmonary Function Test (Breathing Test)			

Question 6

Did your child have any breathing problems in the PAST?

☐ NO

☐ YES **:** ……..

(which lung problems? - see list in question 4 / at which age and how often?)

Question 7

Does your child have any lung problems TODAY?

☐ NO

☐ YES **:**

c) Please describe your child's lung problems:

- **Trouble breathing** or **asthma** ……..……..…..……..
  (how often per year? how long each time?)
- **Infections of the lung** (pneumonia, bronchitis) ……..……..……..
  (how often per year? how long each time?)
- Chronic or recurrent **cough** ……..……..……..……..
  (how often per year? how long each time?)
- Other**:** ……..……..……..
  (how often per year? how long each time?)

d) How much do these lung problems affect your family life?

- not at all
- mild (some restrictions)
- moderate
- severe (most important problem we have)

Question 8

Do breathing problems limit your child's physical activity?

☐ NO (my child has the same activity level as other children of the same age)

☐ YES (please explain): ……..……..……..……

Question 9

Does your child have any other medical problems?

☐ NO

☐ YES (please explain): ……..……..……..……..……..……

(which problems? since when? for how long?)

Question 10

Does your child need to take any medication?

☐ NO

☐ YES **:**

Medication's name	Dose	For what?	Since when? (how old was your child when first prescribed?)

Question 11

How would you rate your child's overall health?

- ❑ excellent
- ❑ good (well more than 60% of the time)
- ❑ fair
- ❑ poor (chronically ill)

Question 12 - about your child's BIRTH:

a) **What was your baby's birth weight** (pounds or grams) **:** ……..……..……..……..

b) **Was your baby born on time?**
- ❑ yes, he/she was born at term.
- ❑ no, he/she was born early (pre-term) **:** ……..……..……..……..……
(how many weeks too early? / induced ?)

c) **Did you have a Cesarean Section or was it a vaginal delivery?** ….……..……...

d) **Did your baby have any breathing problems soon after birth?** ….……..……

e) **How was your baby's health in the first few weeks after birth?**
- ❑ excellent
- ❑ good (more than 60% of the time well being)
- ❑ fair
- ❑ poor (chronically ill)

f) **At which hospital was your child born? :** ……..……..……..……
(hospital's name, city & state)

Question 13 - about your child's development BEFORE BIRTH:

a) **When was the lung mass first detected:** ……..……..……
(at which gestational week?)

b) **When was the last prenatal ultrasound before birth?:** ……..……..…
(at which gestational week?)

c) **Did the lung mass change during pregnancy?**
- ❑ stayed the same size (same)
- ❑ became bigger (worse)
- ❑ became smaller (better)
- ❑ disappeared (best)

d) **At which hospital or obstetrician's office were the prenatal ultrasounds done?:**……..

……..……..……
(obstetrician's and/or hospital's name, city & state)

Important Last Administrative Question 14

May we contact YOU and your CHILD'S doctors and/or hospitals (medical records department)?

☐ NO

☐ **YES, my child's name is:** ……..……..……...……..……..…..…
(full name)

☐ **YES, you can contact me:** my telephone number is: (……)……..……...……..……..…
(please include area code)

☐ **YES, you can contact following doctors:** (please include the phone numbers if available)

Hospitals or Doctors: (same than in previous questions ?)	**Name:**	**State / City:**	**Phone Number:** (please include area code)
Pediatrician (who cares for your child now)			
Obstetrician's office or **Hospital** at which the **prenatal ultrasounds** were done			
Hospital at which the **"X-rays"** were preformed **after birth**			
Hospital at which your child was **born**			
Hospital at which the **lung surgery** was performed			

IS THERE ANYTHING MORE YOU WANT TO TELL US OR SEND US?

(Thank you very much for all your assistance! We will fully reimburse your additional mailing costs upon request.)

- Please use the following space to tell us anything more about your child and his/her well-being or illness.
- Please feel free to send us any more documents about your child (e.g. photos, medical record copies, ultrasounds, etc.).
- Please feel free to call your obstetrician and/or pediatrician and/or the medical record department of your child's hospital to send us copies of your child's prenatal ultrasound-reports or ultrasound-tapes and/or information about your child's imaging studies after birth, as well as reports from birth, lung surgery and respiratory problems (if UCSF was not your caretaker).
- Do you have any comments about this study?

Telephone Script for Calls to Parents
who did not decline and who did not return the written questionnaire:

Good morning / afternoon;
are you Ms / Mr. … *(family's name)* ? *(for re-confirmation)*
My name is Eva Bartsch, I am a medical student calling on behalf of Doctor Diana Farmer and Doctor Ruth Goldstein from the Fetal Treatment Center from the University of California, San Francisco.
Did you receive a letter from us we send you 3 weeks ago?

1) If parents say YES that they received the letter:
We would like to remind you that we are conducting a survey to find out more about how children who were diagnosed before birth with Congenital Cystic Adenomatoid Malformation of the Lung (CCAM) are doing later in life. The knowledge we hope to gain with this study will help us to counsel parents in the same situation you were in when referred to our Fetal Treatment Center during pregnancy.

Your participation in this study is very important to us and we would appreciate your contribution very much. If your child did not survive we want to express our deepest sympathy and we would be very grateful about your partaking.

You may know from our letter that we would like to ask for your help in this study by answering some questions over the phone about your child's health in the form of a questionnaire. This will take approximately 5-10 minutes. If you agree we also would like to review your child's medical records and call your pediatrician for some last questions, if you provide us with your pediatrician's address and phone number. That's it; no other information will be collected.

Do you know from our letter that your data will be handled confidentially and that participation in research is voluntary?
(if parents do not know about these issues, I will read the appropriate paragraphs from our 'Parents Recruitment Letter' to them)

Do you have any questions?
Do you have the telephone number we sent you in case you have questions later?
(if parents do not have our numbers we read them from our 'Parents Recruitment Letter')

(continuation see below)

2) If parents say NO that they did not receive the letter:
I am sorry about that; we wrote in the letter, that we are conducting a survey to find out more about how children who were diagnosed before birth with Congenital Cystic Adenomatoid Malformation of the Lung (CCAML) are doing later in life. The knowledge we hope to gain with this study will help us to counsel parents in the same situation you were when referred to our Fetal Treatment Center during pregnancy.

Your participation in this study is very important to us and we would appreciate your contribution very much. If your child did not survive we want to express our deepest sympathy and we would be very grateful about your partaking.

We would like to ask for your help in this study by answering some questions over the phone about your child's health in form of a questionnaire. This will take approximately 5-10 minutes. If you agree we also would like to review your child's medical records and call your pediatrician for some last questions, if you provide us with your pediatrician's address and phone number. That's it; no other information will be collected.

(then I read paragraph five, six and the first and last sentence of paragraph seven of the 'Parents Recruitment Letter' to the parents on the phone)

Continuation of 1) and 2) for both, parents who say YES that they received the letter and parents who say NO that they did not receive the letter:
We would appreciate your consent very much. Do you want to take part in the study and give your verbal consent to proceed?
(If parents hesitate to answer I can ask them if they need more time for decision making and that I could call back later or make an appointment to call back later)

If parents say NO to consent:
We apologize very much for taking your time and we will not contact you again.
Do you want to take our telephone number to call us back in case you have some questions or you decide to take part in the study later?
(➔ our study phone number (510) 681-8160)
We wish you a good day. Good-bye.

If parents say YES to consent:
Do you want to answer the questions about your child's health now or do you want me to call back later or make another appointment on the phone? *(➔ date/time?)*

(If parents say ***again YES*** *to answer questions now:)*
The Questionnaire about your child's health contains **13** questions, some of them with sub topics. The first question is: … *(see attached 'Parents Questionnaire')*…

(if parents answer in question 1b that their child passed away we again express our deepest sympathy to them before proceeding with the questionnaire)

(at the end of the questionnaire) Thank you very much for your time and cooperation. Do you have any further questions or do you want any of our numbers again to contact us later? *(➔ numbers as above)* Have a good day. Good-bye.

(If I did an appointment with parents and I call them a second time, then I introduce myself again and I remind them about having made an appointment with us at this time/date before I start with the 'Parents Questionnaire')

COMMITTEE ON HUMAN RESEARCH
OFFICE OF RESEARCH ADMINISTRATION, Box 0962
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
www.ucsf.edu/ora/chr

CHR APPROVAL LETTER

TO: Diana L. Farmer, M.D.
Box 0570

RE: Outcome of Fetuses with Congenital Cystic Adenomatoid Malformation of the Lung

The Committee on Human Research (CHR) has reviewed and approved this application to involve humans as research subjects. This included a review of all documents attached to the original copy of this letter. The CHR is the Institutional Review Board (IRB) for UCSF and its affiliates. UCSF holds Office of Human Research Protections Federalwide Assurance number FWA00000068. See the CHR website for a list of other applicable FWA's.

APPROVAL NUMBER: H5881-19172-01 . This number is a UCSF CHR number and should be used on all correspondence, consent forms and patient charts as appropriate.

APPROVAL DATE: October 31, 2001. **Expedited Review**

EXPIRATION DATE: October 31, 2002. If the project is to continue, it must be renewed *by the expiration date.* See reverse side for details.

ADVERSE EVENT REPORTING: All problems having to do with subject safety must be reported to the CHR within ten working days. All deaths, whether or not they are directly related to study procedures, must be reported. Please review Appendix A of the CHR *Guidelines* for additional examples of adverse events or incidents which must be reported.

MODIFICATIONS: Prior CHR approval is required before implementing any changes in the consent documents or any changes in the protocol which affect subjects.

QUESTIONS: Please contact the office of the Committee on Human Research at (415) 476-1814 or campus mail stop, Box 0962, or by electronic mail at chr@research.ucsf.edu.

Sincerely,

Reese T. Jones, M.D.
Chair
Committee on Human Research

cc: Eva Bartsch, Box 0570

COMMITTEE ON HUMAN RESEARCH
OFFICE OF RESEARCH ADMINISTRATION, Box 0962
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
www.ucsf.edu/ora/chr

CHR APPROVAL LETTER

TO: Diana L. Farmer, M.D.
Box 0570

Ruth B. Goldstein, M.D.
Box 0628,

RE: Outcome of Fetuses with Congenital Cystic Adenomatoid Malformation of the Lung

The Committee on Human Research (CHR) has reviewed and approved this application to involve humans as research subjects. This included a review of all documents attached to the original copy of this letter.

The CHR is the Institutional Review Board (IRB) for UCSF and its affiliates. UCSF holds Office of Human Research Protections Federalwide Assurance number FWA00000068. See the CHR website for a list of other applicable FWA's.

APPROVAL NUMBER: H5881-19172-02. This number is a UCSF CHR number and should be used on all correspondence, consent forms and patient charts as appropriate.

APPROVAL DATE: September 17, 2002. **Expedited Review**

EXPIRATION DATE: September 17, 2003. If the project is to continue, it must be renewed by the expiration date.

GENERAL CONDITIONS OF APPROVAL: Please refer to www.ucsf.edu/ora/chr/gen_cond_appvl.htm for a description of the general conditions of CHR approval. In particular, please note that prior CHR approval is required before implementing any changes in the consent documents or any changes in the protocol unless those changes are required urgently for the safety of the subjects.

QUESTIONS: Please contact the office of the Committee on Human Research at (415) 476-1814 or campus mail stop, Box 0962, or by electronic mail at chr@research.ucsf.edu.

Sincerely,

Reese T. Jones, M.D.
Chair
Committee on Human Research

cc: Eva Bartsch, Box 0570

BH

UCSF FETAL TREATMENT CENTER

513 PARNASSUS AVENUE,
ROOM 1601 HSW
SAN FRANCISCO,
CA 94143-0570

OFFICE: 1-800-RX-FETUS
FAX: (415) 476-2314
WEB: fetus@USHC.org

RE: Annual Renewal and Minor Modification of the Expedited Subcommittee Reviewed Research Study with the CHR approval number: **H5881-19172-01** from Doctor Diana Farmer (PI) entitled "Outcome of Fetuses with Congenital Cystic Adenomatoid Malformation of the Lung (CCAM)".

EZ

Dear Committee of Human Research

CBB

This letter is to apply for annual renewal and minor modification of the research study H5881-19172-01. The letter includes the specific requested information for the CHR status report for renewal application and the explanation for the minor modifications we applied to the questionnaire, as well as the only inserted change we applied to the recruitment letter followed by the same change in the study protocol. All other contents of the recruitment letter and of the study protocol stay the same. No other documents are altered.

The only Minor Modification of the Recruitment Letter and Study Protocol:

(a) The only modification applied to the parent recruitment letter is to specifically address parents of children with Pulmonary Sequestration (PS) as well as parents of children with CCAM in the first paragraph of the recruitment letter. These two congenital fetal lung lesions are similar and prenatal as well as postnatal differential diagnosis is difficult in some cases. We are thankful to parents, who brought up this issue after we sent the first mass mail. We were aware of considering PS cases when studying CCAM cases, since we may not be able to distinguish both diseases at first. That is why we wrote in the CHR protocol about general "congenital lung lesions, such as CCAM". To thoroughly study CCAM cases we have to consider the PS cases as well. Thus we replaced the word "CCAM" with "CCAM or PS" in the study title and at any other location in the study protocol. Even though there is no change in any of the protocol contents. The study aim, the procedure & consent process and the risks stay the same.

Minor Modifications of the Parents Questionnaire:

(b) Most changes made in the parents questionnaire focus on gathering more objective information from medical records by asking the parents to provide us with addresses and phone numbers of the hospitals and doctors involved in the care of the child and to allow us to contact them, e.g. obstetricians for prenatal data, pediatric surgeons for information about operations and hospitals where the child was born or postnatal imaging studies were done (see changes in the instruction and in questions 4, 5, 12, 13 and 14). As we progressed in our study we realized, as a referral center for fetal diseases we provide the prenatal evaluations, but many of these patients are followed at their referral hospitals, which explains the lack of objective medical record data of some of our patients.

(c) We added some questions about the prenatal course to evaluate how the parents assess the situation before birth (see question 13 and 5).

(d) We learned from the patients feed back about valuable material some parents provided us with and asked for these documents in the last optional question "Is there anything more you want to tell us or send us?"

(e) We changed the sequence of the questions as we thought it might be more convenient for the parents (see highlighted question numbers).

(f) All changes are highlighted on the printout together with the replacement of the word "CCAM" with "CCAM and PS" in the first sentence and some trivial adjustments not mentioned here.

The proposed modifications do not change the risks of loss of privacy and confidentiality and the potential inconvenience for the parents in taking part in the questionnaire and phone calls. The measures undertaken to minimize these risks stay the same. Benefits for fetal diagnosis and treatment of future patients will most likely increase following the modifications, since we will be able to gather more and even more objective data.

For the Annual Renewal Status Report:

(a) **Protocol Summary:** The long-term objective of our study is to better counsel parents with fetuses with congenital lung lesions, such as CCAM or PS. The specific aims include elucidation of the natural history of these lesions during the prenatal period and the development of the mass after birth before lung surgery. We want to find out if there are specific prenatal sonographic parameters predictive to the outcome of the fetuses. We also want to know how the children are doing later life with and without surgery. Therefore we conduct a long term outcome study (retrospective cohort study) by sending questionnaires to parents of affected children and reviewing the mothers' and children's medical records.

(b) **Summary of Results:** We analyzed the data of 28 patients who sent back the filled out questionnaire and reviewed their medical records regarding prenatal ultrasounds and pre-and postnatal outcome, if available. The results show a tendency of large lung lesions doing worse, that means children needed surgery or even died. However we wonder about some large lesions in the study showing favorable outcome even without surgery and some lesions which decreased before or after birth. We observed a similar phenomenon for prenatally diagnosed mediastinal shift. Up to this point our results are not statistically significant, because we need more patients involved in the study.

(c) **Summary of Recent Literature:** In the last 10 years 23 clinical studies were published about the outcome of children prenatally diagnosed with CCAM or PS. However, the published studies lack adequate number of cases and long term follow up. Only four of them evaluated more than 25 patients looking mainly at perinatal outcome. The 2 new clinical studies brought out in the last year (2001) dealt again with less than 15 patients. We intend to evaluate more than 90 patients and our follow up interval reaches 13 years so far. There is no alteration of the risks involved in our retrospective cohort study (see also next paragraph). Results of the above mentioned literature is not changing the risk either.

(d) **Reanalysis of Risk/Benefit Ration:** As we pointed out in the last paragraph about our questionnaire modifications, the risks of loss of privacy and confidentiality and the potential inconvenience for parents of taking part in the questionnaire do not change. The measures undertaken to minimize this risks stay the same. Yet the benefits for fetal diagnosis and treatment of future patients will most likely increase by continuing the study and collecting more patients' data with the modified questionnaire. We expect to find statistically significant results and formulate a message to our obstetric colleagues, who still consider large lung lesions as lethal.

(e) **Brief Summary of Plans for the Coming Year:** We plan to involve at least 62 more patients in the study by sending out a second mass mailing to more patients and follow up on patients by phone who do not respond. As soon as we receive the mothers' consent we go ahead and examine the medical records. By analyzing the patients' data with the assistance of our statistician we look forward to find significant results and knowledge about prognosis and treatment of CCAM and PS.

If there are any further questions, please do not hesitate to contact us.

Sincerely,

Diana Farmer, MD, PI
Department of Surgery
and Fetal Treatment Center, UCSF
Box 0570, HSW 1601, 513 Parnassus Ave
Office phone: 472-7387

Ruth Goldstein, MD, Co-PI
Department of Radiology
and Fetal Treatment Center, UCSF
Box 0628, Moffit 396, 505 Parnassus Ave
Office phone: 476-1397

Eva Bartsch, I
Medical Student
Fetal Treatment Center, UCSF
Box 0570, HSW 1601, 513 Parnassus Ave
Study phone: (510) 6818160

8/27/02

RENEWAL OF SUBCOMMITTEE REVIEWED STUDY
(CHR approval number: H5881-19172-01; Category #7)

OUTCOME OF FETUSES WITH CONGENITAL CYSTIC ADENOMATOID MALFORMATION OF THE LUNG OR PULMONARY SEQUESTRATION

Study Aim:

With the increased use of prenatal ultrasonography, a large number of congenital lung lesions such as congenital cystic adenomatoid malformation (CCAM) or pulmonary sequestration (PS) have been identified before birth. Prenatal natural history of CCAM and PS ranges from fetal death to complete in utero regression. The neonatal outcome of these fetuses also ranges from life-threatening respiratory distress to asymptomatic presentation. The prognostic factors involved in the diverse outcome of fetuses with CCAM and PS are not well understood, making the counseling of parents and management decisions difficult. Previous clinical studies lack adequate number of cases and long term follow up. The Fetal Treatment Center at UCSF has accumulated over 170 prenatally diagnosed CCAM and PS cases since 1987. Our plan is to review the prenatal ultrasonographic findings and correlate these findings with the outcome of the children. The aim of this retrospective study is (1) to identify prenatal factors that may predict (long term) outcome and (2) to potentially clarify the indications for prenatal and postnatal treatment.

Subject Population:

The subject population to be studied consists of patients prenatally diagnosed with congenital cystic adenomatoid malformation (CCAM) or pulmonary sequestration (PS). All of theses patients by the nature of their disease are fetuses and children. The oldest child should be 14 years old, since fetuses with lung lesions have been referred to our Fetal Treatment Center (FTC) at UCSF since 1987. The FTC database will be used to identify eligible patients. Patient's data may also be collected from the Pediatric Surgery database and/or Neonatal Intensive Care Nursery database when postnatal care occurred at UCSF. Approximately 170 patients will qualify for our study. We do not intend to contact the children in this study, instead we will correspond with their parents and pediatricians to request follow up information. We will contact the parents in written form, sending a questionnaire about their child's health (see attached parent questionnaire). If parents do not respond after 3 weeks, we will contact them by phone. If the parents consent, we will call their pediatricians (see attached pediatrician questionnaire). In the event that parents are non-English speaking we have translators in our own investigative team.

Procedures to be done:

The study consists of two parts, (1) a retrospective medical records review and (2) an interview of the patients' parents and their pediatricians by means of a written questionnaire. No other procedures will be done. The medical records include records from our Fetal Treatment Center (FTC) database, Pediatric Surgery database, and the UCSF hospital chart and ultrasound images. Specific parameters (see attached datasheet) will be collected from these medical records and stored in research records under

randomly assigned numbers. Only with the patient's assent (parent consent), we will review the previous-mentioned records. The first contact with the parents will be in written form. We will send them a recruitment letter, an information sheet, a parent questionnaire and a refusal postcard (see attachments). The estimated time needed to read the documents and to answer the questionnaire is about 5 - 10 minutes. If parents do not sent us back the filled out questionnaire or the refusal postcard after 3 weeks, we will call them to obtain consent (with the same wording in the recruitment letter and information sheet) and then obtain the answers to the previously sent questionnaire. After consent is received we will call the pediatricians for further information (see pediatrician questionnaire), which would take around 5 - 10 minutes of the pediatrician's time. No costs accrue to the parents or pediatricians. The expenses for mail and phone calls will be covered by the study. Since this is a student project we want to keep expenses as low as possible. We would like to restrict our correspondence to one mailing to the parents and one phone call to the pediatricians and if necessary one additional phone call to the parents. This strategy will minimize inconveniences to the study participants.

Risks:

The two risks involved in this study are the potential of loss of privacy and confidentiality and the possible inconvenience in taking part in a questionnaire and phone interview. The parents may experience discomfort related to some of the questions concerning the health and well being of their child. There is no way that patients remain anonymous during the process of this study. In order to receive the patients' medical records and make contact with them and their pediatricians, we have to utilize their names, addresses, phone numbers and medical record numbers. However utilizing this information will be restricted to the investigators listed on the CHR cover page. To minimize the risk of loss of privacy and confidentiality, the following precautions will be undertaken: (1) Names, addresses, medical record numbers or other sensitive data will be excluded from our research data base, (2) patients will be referred to by randomly assigned numbers, (3) questionnaires and refusal postcards are marked with the same randomly assigned number only, (4) the research data base will be stored in a Microsoft Excel spreadsheet, and (5) participants' names or other identifying data will also be excluded from any potential presentation or publication. Access to patients' identifiable data (a separate Excel datasheet with the randomized numbers and the participants identifying data) is strictly limited to the investigators listed on the CHR cover page. They keep control over contacting the parents and pediatricians, who gave consent and who denied participation, so any inquiry is stopped immediately in case of denial or once the information is received. To minimize parental discomfort through an interview, we (1) will initially contact them in written form to provide information about us and our study and their right to refuse participation in all or parts of the study (see section "procedures" and attachments), (2) reduce time consume by keeping documents as short as possible and mail them at once (see section "procedures" and attachments), and (3) arrange any phone calls at the time most convenient for the participants. No costs accrue to the subjects, since the expenses for mail and phone calls will be covered by the study. With these precautions we hope to keep the aforementioned risks as little as possible and give the participants the best experience with this study and clinical research in general.

Benefits:
Results from this study will benefit medical science, in particular the growing field of fetal diagnosis and treatment. Significant knowledge, based on data collected from a tertiary referral center for fetal diseases with 14-years of experience, will be gained. The beneficial knowledge includes: (1) outcome of fetal lung lesions, in particular of congenital cystic adenomatoid malformation of the lung (CCAM) and pulmonary sequestration (PS), (2) determination of crucial prognostic factors for fetuses with CCAM and PS by means of prenatal ultrasonography, and (3) elucidation of indications for prenatal and postnatal treatment of CCAM and PS. We anticipate better and more informed counseling of parents with fetuses suffering from CCAM or PS lung lesions. There is no direct benefit for the individual participant. However, the parents may feel satisfied after taking part in the study. Parents who are referred to the Fetal Treatment Center are typically proactive and very engaged and they may gain satisfaction from helping to find more precise indicators for outcome and treatment of unborn children with the same disease as their child.

Consent Process and Documentation:
Herewith we apply for a CHR approval of waiver of signed consent to conduct the informed consent process through use of an information sheet. There are four reasons to do so: (1) our study involves no more than minimal risk (category #1), (2) the identities of the subjects will be completely anonymous after the information for the research records is obtained (category #1), (3) the risks of loss of privacy and confidentiality and inconveniences for the participants will be lessen in this way, and (4) the rights and welfare of the subjects are not adversely affected without a signed consent. The patients' freedom to participate in the study or to denial participation will be guaranteed (1) in form of a written refusal postcard attached to the information sheet, since the initial contact is made in written and (2) again in verbal form during the following phone call, if patients did not answer in written form. To offer more choices and flexibility to the participants, they can refuse to take part in all or only some parts of the study. Furthermore, they can decide to participate in written form only by sending back the filled out parent questionnaire if they do not want to be contacted in person, or they can simply answer in verbal form on the phone, in case they do not want to write. Please refer to the attached recruitment letter and information sheet, which includes all elements of the consent document.

Qualifications of Investigators:
The principle investigator is Doctor Diana L. Farmer, UCSF Associate Professor of Surgery and Pediatric Surgeon. Co- principle investigator is Doctor Ruth B. Goldstein, UCSF Professor of Radiology and Obstetrics & Gynecology. They will mentor the investigative team, consisting of Eva Bartsch, visiting scholar and medical student in the final year from the University of Cologne, Germany and collaborator at the UCSF Fetal Treatment Center and Doctor Alexander Strauss, Assistant Professor of Obstetrics & Gynecology from the University of Munich, Germany. All of these investigators have a particular interest in prenatal diagnosis and treatment and Pediatric Surgery.

Curriculum Vitae

Persönliche Daten

Name	Eva Maria Pott Bärtsch
Geburtsdatum, -ort	14. September 1964, Köln
Familienstand	verheiratet, ein Kind

Medizinische Forschungsarbeiten und Publikationen

bis 2009	**Ludwig-Maximilians-Universität München, Medizinische Fakultät**: Doktorandin (Rigorosum 07/2009)
2000 – 2005	**Fetal Treatment Center Laboratory**, **University of California, San Francisco, USA**: Wissenschaftliche Mitarbeiterin
02/2006	Phaloprakarn* C, **Pott Bärtsch*** **EM**, Harrison MR. Residual congenital cystic adenomatoid malformation and thoracic scar deformation after fetal surgery: a case report. J Pediatr Surg 2006; 41: e11-e14 (*equal first authors)
12/2003	Muench MO, **Pott Bärtsch EM**, Chen JC, Lopoo JB, Barcena A. Ontogenic changes in CD95 expression on human leukocytes: prevalence of T-cells expressing activation markers and identification of CD95-CD45RO+ T-cells in the fetus. Dev Comp Immunol 2003; 27: 899-914
01/2003	**Pott Bärtsch EM**, Paek BW, Yoshizawa J, Goldstein RB, Ferrell LD, Coakley FV, Harrison MR, Albanese CT. Giant fetal hepatic hemangioma. Case report and literature review. Fetal Diagn Ther 2003; 18: 59-64

Berufliche Fortbildungen und Interessensgebiete

2008 – 2009	Fortbildungen in Sozialer-, Interkultureller- und Forensischer Psychiatrie, Systemischer Familientherapie und Neurologie an der Psychiatrischen LVR-Klinik Langenfeld
2006 – 2008	Fortbildungen in den Kliniken für Psychiatrie, Psychosomatik und Psychotherapie und Kinder- und Jugendpsychiatrie der Universität zu Köln
2000 – 2003 und 1996	Fortbildungen in Pädiatrie, Chirurgie, Kinder- und Fetenchirurgie und Pränataldiagnostik am Universitäts- und Kinderspital Zürich, Schweiz, und an der University of California, San Francisco, USA
1997 und 1995	Fortbildungen am Institut für Geschichte und Ethik der Medizin, Universität zu Köln

Klinische Tätigkeit als Ärztin

2008 – 2009 **LVR-Klinik Langenfeld, Landschaftsverband Rheinland** (Dtsch. Approbat. 10/2007): Stationsärztin in der Abteilung für Gerontopsychiatrie und Neurologie (geschlossene Aufnahme- und Behandlungsstation für Demenzkranke) und in der Abteilung für Suchtkrankheiten (Aufnahmestation für Alkohol- und Medikamentenabhängige)

Praktisches Jahr

01-05/2000 **University of California, San Francisco (UCSF) School of Medicine, USA**: Division of Pediatric Surgery of the Department of Surgery

07/1999 - 10/1999 **Stanford University School of Medicine, California, USA,** Department of Internal Medicine: Divisions of Cardiology, Nephrology and Gastroenterology

02/1999 - 06/1999 **Kinderspital Zürich, Schweiz**, Departement Pädiatrie: Medizinische und Kinderchirurgische Kliniken, Zentrum für brandverletzte Kinder, Rehabilitationszentrum für Kinder und Jugendliche

10/1998 - 02/1999 **Universitätspital Zürich, Schweiz**, Departement Chirurgie: Kliniken für Unfallchirurgie, Herz- und Gefäßchirurgie, Wiederherstellungs- und Handchirurgie, Verbrennungszentrum und Polytrauma Zentrum

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