Received: 1 April 2020 | Revised: 23 May 2020 | Accepted: 1 June 2020

DOI: 10.1111/aogs.13933

ORIGINAL RESEARCH ARTICLE

Prenatal ultrasound and magnetic resonance evaluation and fetal outcome in high-risk fetal tumors: A retrospective single-center cohort study over 20 years

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Abstract

Introduction: Fetal tumors are rare and usually followed by poor outcome. We describe our single-center experience with fetal tumors evaluated by ultrasound and magnetic resonance imaging (MRI). Our aims were to evaluate mortality and morbidity including long-term outcome and to determine which ultrasound and MRI characteristics were helpful for pre- and perinatal management.

Material and methods: We conducted a retrospective analysis on prenatally diagnosed tumors between 1998 and 2018. Poor outcome included fetal or neonatal death and survival with serious illness. MRI addressed tumor morphology (sacrococcygeal teratomas), compromise of surrounding structures (head and neck tumors) and early depiction of brain alterations specific to tuberous sclerosis (rhabdomyomas).

Results: Of 68 pregnancies, 15 (22%) were terminated and eight children (8/53, 15%) died pre- or postnatally. Of the 45 survivors (45/68, 66%), 24 (24/45, 53%) were healthy, eight (8/45, 18%) had a minor illness and 13 (13/45, 29%) a serious illness. Diffusion- and T1-weighted MRI reliably predicted tumor morphology in teratomas. To detect head and neck tumors critical to airway obstruction, MRI was superior to ultrasound in delivery planning. Rhabdomyomas were frequently associated with tuberous sclerosis, regardless of their number or size in ultrasound; MRI could depict specific brain alterations from the early third trimester onwards. For several rare tumors, MRI provided critical differential diagnoses that could not be clearly displayed in ultrasound.

Conclusions: The rate of survivors with serious long-term illness among fetuses with prenatal diagnosis of a tumor was high. MRI is specifically helpful for risk stratification in fetal teratomas and delivery planning in head and neck tumors.

KEYWORDS

fetal magnetic resonance imaging, fetal oncology, fetal ultrasound scan, outcome prediction, prenatal diagnosis

Abbreviations: EXIT, ex utero intrapartum treatment; MRI, magnetic resonance imaging; RM, rhabdomyoma; SCT, sacrococcygeal teratoma; TSC, tuberous sclerosis complex.

1 | INTRODUCTION

Fetal tumors are rare and usually characterized by poor outcome.[1] Mortality and morbidity depend on tumor specificity, hemodynamic compromise and gestational age at delivery.[2,3] Fetuses may be considered unstable and therefore at risk of premature delivery at an unfavorable birthweight, or referred to a center that offers prenatal surgical intervention.[4-9] Delivery at a center with nearby neonatal oncology services may or may not improve outcome of fetuses with rare malignancies,[10,11] but only a few centers worldwide take an overview of large series of similar intrauterine patients to establish protocols for perinatal treatment.[1,5,8,12]

Currently, there is little data available on the prenatal multimodal and multiparametric imaging as well as the clinical course of fetal tumors. Thus, the benefits of detailed prenatal magnetic resonance imaging (MRI) as well as ultrasound with regard to pre- and perinatal management and possible associations with outcome are currently unclear. Due to the complementary nature of MRI and ultrasound, this study tried to take advantage of combining third level ultrasound and high quality multiparametric fetal MRI using dedicated imaging protocols, performed at a center with special interest in this field.

The aim of this study was to review all prenatal ultrasound and MRI reports as well as histopathology reports and postnatal follow-up data of fetal tumors prenatally diagnosed in a single-center population in order systematically to evaluate the spectrum of imaging and clinical data together with outcome over the last 20 years.

Key message

Severe morbidity is common among survivors of prenatally diagnosed tumors. MRI is helpful for risk stratification in fetal teratomas and delivery planning in head and neck tumors. Specific brain alterations in tuberous sclerosis are only seen in the third trimester.

2 | MATERIAL AND METHODS

2.1 | Study design and patients

We conducted a retrospective single-center cohort study at the Medical University of Vienna involving three departments (Department of Obstetrics and Fetomaternal Medicine, Clinical Institute of Pathology, Department of Radiology with focus on fetal imaging) to review all cases of prenatally suspected and postnatally confirmed fetal tumors between 1 January 1998 and 31 December 2018.

In total, 83 cases of fetal tumors in singleton and multiple pregnancies were found in this study period. Inclusion criteria for in-depth analysis were a postnatally confirmed diagnosis of a prenatal teratoma, rhabdomyoma (RM), lymphangioma or solid/vascular adrenal, hepatic, cardiac or cerebral tumor. We intentionally did not include common pulmonary malformations or cystic lesions of the ovaries. Records of fetuses were excluded that had been evaluated only once, if the tumor could not be detected on follow-up scans or when no postnatal data were available.

2.2 | Standard procedures

As a tertiary referral center we have a high frequency of pregnant women referred for further evaluation of suspected fetal malformations. Our practice guidelines follow the standard procedures as defined by the Fetal Medicine Foundation and International Society of Ultrasound in Obstetrics & Gynecology (ISUOG). Fetuses had a detailed sonographic assessment including fetal echocardiography and Doppler assessments of fetal hemodynamics at their initial visit and during prenatal follow-up visits. Ultrasonographic evaluations of fetal tumors and fetal echocardiography were performed by obstetricians/fetal medicine specialists with at least 10 years of experience in ultrasonography for fetal diagnosis and therapy, following the ISUOG recommendations on fetal echocardiography.[13] Transabdominal as well as transvaginal two- and three-dimensional neurosonography was routinely performed for in-depth assessment of axial, coronal and sagittal planes of the fetal brain. Genetic testing was offered in all cases, preceded by extensive genetic counseling.

Sonographic variables assessed were exact tumor dimensions, number and dimension of blood vessels within the tumor (if feasible), morphology, and location, structural and functional interferences with surrounding organs, assessment of cardiac anatomy and hemodynamic function, the presence or absence of additional malformations, fetal growth, assessment of amniotic fluid volume, and search for fetal functional impairment specific for the tumor location. When the tumor was considered lethal or at high risk of serious postnatal morbidity, the parents were offered termination of pregnancy. For ongoing pregnancies, follow-up visits with full re-evaluation of tumor and fetal growth as well as cardiac monitoring and Doppler measurements for high cardiac output physiology were scheduled every 2-4 weeks depending on tumor characteristics and fetal well-being. When any of the indices showed an increase in risk and the potential of emerging fetal demise, lung maturation was induced.

At our center, fetal MRI (1.5 Tesla) has been offered as standard for additional evaluation for the last 15 years. Multiplanar T2-weighted Turbo Spin Echo sequences and T1-weighted sequences using breath hold were acquired. In most cases, diffusion weighted and echo planar sequences were also available.

When imaging results revealed a high likelihood of airway obstruction by the growing tumor, the preferred delivery mode was an elective cesarean section with the ex utero intrapartum treatment (EXIT) procedure[12,14]: For the EXIT procedure, maternal laparatomy was performed in the standard Pfannenstiel fashion and hysterotomy was planned such that the placenta was avoided, using uterine staplers with absorbable staples to maintain hemostasis. After exposure of the fetal head and following intramuscular administration of fetal

anesthetic the intubation, or eventually tracheostomy, was performed by the neonatologist or the pediatric surgeon. The fetus was monitored using pulse oximetry and ultrasound examination of the heart rate. Once the fetus was successfully ventilated, the fetal body was delivered and the umbilical cord clamped. The neonate was then immediately taken over by the neonatologist and the pediatric surgeon for further interventions.

2.3 | Research methods

For the purpose of this study, sonographic images were reviewed by two fetal medicine specialists (D.M. with 8 years and B.U. with more than 20 years of expertise in fetal ultrasound) who were blinded for outcome. In terms of the MRI images, all investigations followed the guidelines for fetal MRI examinations.[15,16] Fetal MRIs were re-evaluated for this study by two independent radiologists blinded for pathology records and fetal outcome (G.D. with 3 years and GK with more than 10 years of expertise in fetal MRI).

Sacrococcygeal teratomas (SCT) were classified based on Altman tumor type.[2,17] MRI was used to assess the respective signal components of the tumor, allowing differentiation between more cell-dense and less cell-dense parts, the content of cystic structures, to determine the organ of origin, and to evaluate respective consequences, eg tracheal occlusion.

Tumor-fetal ratio was calculated on the basis of ultrasound records.[2,3,9,18] For fetal SCTs we assessed tumor-fetal ratio, tumor classification, the ratio of cystic to solid components, the presence of hydrops, and/or early delivery to outcome.[4,5,18]

Prenatal ultrasound and MRI were compared with long-term outcome data to evaluate which diagnostic approaches best predicted the tumor's specific prognosis. MRI was considered to provide additional information or improve diagnostic accuracy after ultrasound, when the multiplanar MRI approach allowed a less distorted visualization of the specific tumor boundaries, thus allowing a better planning of future surgery and/or suspicion of immaturity or invasive tumor growth. In SCT, diffusion restriction suggested tumors of high cellularity/immaturity. In the case of cardiac tumors, MRI was considered to provide additional information when subependymal heterotopias were depicted on cerebral MRI which had not been visualized on targeted neurosonography. Average length of follow up was 92 months for SCTs, 86 months for teratomas other than SCT (non-SCT), 77 months for RM, and 46 months for lymphatic malformations.

2.4 | Definitions

"Severe illness" was defined as survival with multiple severe mental and physical disabilities. We followed the conceptual definition by Kelley and Bollens-Lund describing "serious illness" as a health condition that carries a high risk of mortality and either negatively impacts a person's daily function or quality of life or excessively strains their caregivers.[19] Tuberous sclerosis complex (TSC), though symptoms can be treated symptomatically, was categorized as severe illness. This categorization was discussed extensively until final agreement, as many people with TSC can live a normal life span. However, severe difficulties, eg uncontrolled epilepsy or complications in the kidneys or the lungs, with a negative impact on the patient's daily function, quality of life and life expectancy, are frequent among patients with TSC. These unpredictable complications, together with the fact that TSC is one of the possible indications for termination of pregnancy in our center, if considered by the parents, lead us to categorize TSC as "severe illness". Minor illness was recorded when the infant's medical records reported temporary therapies such as logo or physical therapy or temporary bladder dysfunction.

For RMs, the number of lesions and the maximum diameter of the largest tumor were obtained from the first sonographic evaluation at our center. We only staged those fetuses as having multiple cardiac tumors who demonstrated more than one RM ab initio. Fetal lymphatic malformations were classified in retrospect according to the suggestions of Oliver et al.[20]

2.5 | Statistical analyses

Due to the small number of cases in each group of tumors, descriptive statistics were applied. Categorical data are given as counts (n) and percentages (%).

2.6 | Ethical approval

Parents' written informed consent was obtained in each case at the time of fetal assessment. The study complied with the principles outlined in the Declaration of Helsinki of 1975, as revised in 2013, and was approved by the institutional review board of the Ethics Committee at the Medical University of Vienna (EK 1883/2019).

3 | RESULTS

Between 1998 and 2018, 83 pregnancies were identified with sonographic suspicion of a fetal tumor; 15 of these cases were excluded, resulting in a study cohort of 68 fetuses (flowchart in Figure 1).

Baseline characteristics and fetal outcomes are summarized in Table 1. Fifteen (15/68, 22%) parents opted for termination of pregnancy and in 8 (8/68, 12%) pregnancies, intrauterine fetal death or neonatal death occurred. Among the remaining 45 (45/68, 66%) survivors, 24 (24/45, 53%) survived with no long-term deficits, 8 (8/45, 18%) children survived with minor illness and 13 (13/45, 29%) children survived with severe illness.

Genetic testing was performed in all fetuses or newborns except for those with head, neck or brain tumors and in the fetus with the heart aneurysm. All children had normal genetic reports except for 10 with defined molecular genetic alterations specific for TSC and RMs and one child with carbamoyl phosphate synthetase

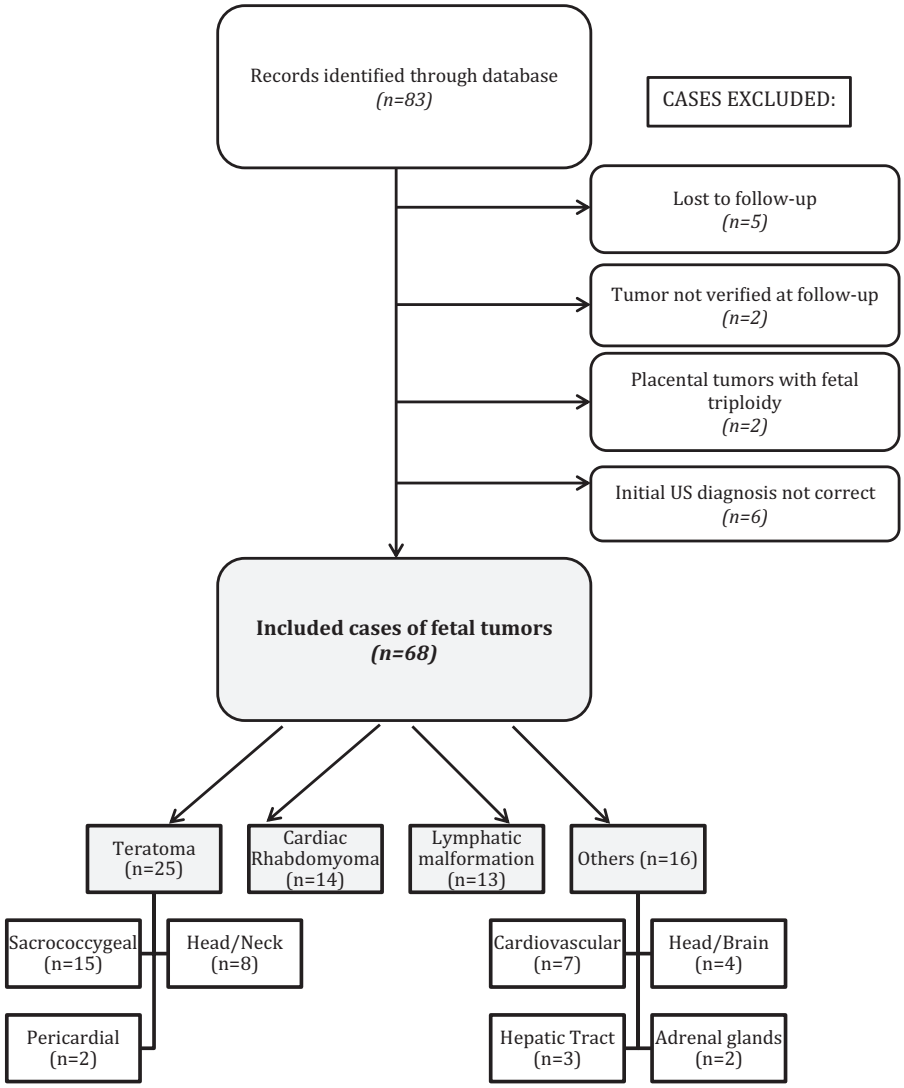

FIGURE 1 Flow diagram on the case selection for study analyses 1998-2018

(CPS1)-deficiency and an eye tumor. Of the 10 fetuses with TSC, five had genetic testing after birth and five antenatally. The five pregnancies with prenatal confirmation of TSC (TSC 1: n = 1, TSC 2: n = 1, unknown type of TSC mutation: n = 3) were all terminated.

Tumor characteristics of SCTs are summarized in Table 2. Two (13%) fetuses developed hydrops and four (27%) had mild polyhydramnios. Three fetuses presented with tumor-fetal ratio >0.12 before 24 weeks, all immature teratomas: One pregnancy was terminated; one had premature rupture of membranes at 26^{+6} gestational weeks, followed by cesarean section of a hydropic infant of 1870 g, who died neonatally; and one non-hydropic fetus was delivered by cesarean section at 28^{+6} gestational weeks and weighed 1200 g after premature rupture of membranes, resulting in a healthy survivor after postnatal resection of the tumor.

Four fetuses with SCT died: one termination of pregnancy, one intrauterine fetal death at 28 weeks, and two neonatal deaths after 26 and 30 weeks' delivery, respectively. Among the five fetuses with early premature delivery before 32 weeks, two neonates died, two (one hydropic, one non-hydropic) are healthy at 18 and 5 years, respectively, and one hydropic fetus with a birthweight of 800 g survived with severe neurodevelopmental delay. In 10 fetuses with SCT, prenatal MRI and postnatal histopathology were available. Diffusion- and T1-weighted MRI allowed a correct prediction in terms of mature or immature SCT in all cases (Figure 2). All children (5/5, 100%) with mature SCTs survived and were healthy. Among the immature SCTs, 2/6 (33%) survived and were healthy, 2/6 (33%) died neonatally, one (17%) survived with serious illness, and one (17%) is currently undergoing chemotherapy.

Ten fetuses presented with teratomas other than sacrococcygeal teratomas (Table 3). Two hydropic fetuses at 27-28 weeks with immature pericardial teratomas were delivered within hours of initial presentation, and both are healthy survivors at 14 years and 14 months of age, respectively, after postnatal resection of their tumors. Among the eight fetuses with teratomas of the head/neck, five parents chose termination of pregnancy (63%). Three fetuses with neck teratoma were delivered at 30-34

TABLE 1 Baseline characteristics and outcome of 68 fetuses included in the analysis, grouped by the prenatal sonographic appearance of the tumor

	US: fetal cardiac decompensation	MRI: added/refined important diagnosis after US	Genetic anomalies	Initial tumor size (US)[a]	TOP or IUFD/ NND	Survival with serious illness	Survival with minor illness	Healthy survivors
Teratoma (n = 25)								
Pericardium (n = 2)	2/2 (100)	2/2 (100)	—	23 cm^3	—	—	—	2/2 (100)
Head/neck (n = 8)	3/8 (38)	4/7 (57)	not tested	180 cm^3	6/8 (75)	2/8 (25)	—	—
Sacrococcygeal (n = 15)	7/15 (47)	10/10 (100)	-	149/0.26	4/15 (27)	2/15 (13)	1/15 (7)	8/15 (53)
Rhabdomyoma (n = 14)	2/14 (14)	5/10 (50)	10/14 (71)[b]	9.8 mm	6/14 (43)	5/14 (36)[b]	—	3/14 (21)
Lymphangioma (n = 13)	1/13 (8)	2/11 (18)	—	7.5 cm	3/13 (23)	—	4/13 (31)	6/13 (46)
Other tumors (n = 16)								
Liver (n = 3)	1/3 (33)	2/3 (67)	—	303/0.08	1/3 (33)	1/3 (33)	1/3 (33)	—
Adrenal (n = 2)	—	2/2 (100)	—	2.3 cm	—	1/2 (50)	—	1/2 (50)
Arterial/venous (n = 6)	2/6 (33)	2/6 (33)	—	3.4 cm	1/6 (17)	1/6 (17)	1/6 (17)	3/6 (50)
CNS (n = 3)	—	2/3 (67)	not tested	3.7 cm	1/3 (33)	1/3 (33)	1/3 (33)	-
Heart aneurysm (n = 1)	1/1 (100)	—	not tested	1.3 cm	—	—	—	1/1 (100)
Solid eye tumor (n = 1)	—	1/1 (100)	CPS1-def.[c]	2.0 cm	1/1 (100)	—	—	—
TOTAL cases	19/68 (28)	32/56 (57)	11/56 (20)	—	23/68 (34)	13/68 (19)	8/68 (12)	24/68 (35)
TOTAL survivors	12/45 (27)	22/45 (49)	5/45 (11)	—	—	13/45 (29)	8/45 (18)	24/45 (53)

Abbreviations: CNS, central nervous system; IUFD, intrauterine fetal death; NND, neonatal death; TOP, termination of pregnancy.

[a]Data are given as numbers (percent). Initial tumor size (US) are given as: cm^3 for pericardial and head/neck teratomas; cm^3/tumor fetal ratio TFR for sacrococcygeal teratomas and liver tumors; largest diameter (mm) for rhabdomyomas/cardiac tumors; largest diameter (cm) for lymphangiomas and other tumors (except liver).

[b]All with tuberous sclerosis complex.

[c]Lethal form of CPS1-deficiency.

TABLE 2 Tumor characteristics, histopathology and outcome data: Sacrococcygeal teratoma

Patient	GA upon presentation in weeks	Tumor type	Initial tumor size, cm^3 (TFR)	Average weekly tumor growth until delivery	US evidence of decompensation, yes/no	Histopathology	Outcome[a]
A	19 5/7	solid, Type I	497 (1.99)	*	No	Immature teratoma	Termination of pregnancy
B	21 4/7	mixed, Type II	30 (0.10)	+44 cm^3	Hydropic	Mature teratoma	30 5/7 CS, 1500 g, healthy 18 yr
C	22 5/7	mixed, Type II	12.8 (0.03)	+6.7 cm^3	No	Mature teratoma	38 2/7 CS, 3470 g, healthy 7 yr
D	20 1/7	mixed, Type IV	12.1 (0.06)	+5.6 cm^3	Increased AF	Mature teratoma	37 6/7 CS, 3520 g, healthy 19 yr
E	20 1/7	mixed, Type II	79.5 (0.22)	+336 cm^3	No	Immature teratoma g^3	26 6/7 CS (PROM), 1870g, NND
F	20 4/7	mixed, Type III	8 (0.03)	+2.4 cm^3	No	Mature cystic teratoma	33 2/2 SD, 2180 g, healthy 5 yr
G	26 2/7	mixed, Type III	110.5 (0.11)	+107 cm^3	Hydropic	Immature teratoma g^3	28 1/7 CS, 800 g, serious illness 7 yr
H	21 1/7	mixed, Type II	260 (0.57)	+40 cm^3	No	Immature teratoma g^3	28 6/7CS(PROM), 1200 g, healthy 5 yr
I	15 3/7	mixed, Type III	1.4 (0.01)	+14.2 cm^3	No	Cystic dysontogenetic teratoma	38 4/7 CS, 3280 g, minor illness 3 yr
J	20 5/7	mixed, Type III	5.3 (0.01)	+4.9 cm^3	No	Mature cystic teratoma	38 CS, 3500 g, healthy 4 yr
K	35	solid, Type III	880 (0.31)	+173 cm^3	Hydramnios	Immature teratoma g^3	38 CS, 4075 g, healthy 1 yr
L	19	mixed, Type II	4.26 (0.01)	+156 cm^3	Increased AF	Immature teratoma g^3	35 1/7CS, 3890 g, chemotherapy 8 mo
M	18 6/7	mixed, Type III	20.9 (0.07)	+23 cm^3	Increased AF	Unknown	Intrauterine fetal death 28 weeks
N	21	mixed, Type II	*	*	No until 30 weeks	Unknown	Born 30 weeks, NND
O	36	solid, Type III	168 (0.08)	*	No	Unknown	39 CS, healthy 15 yr

Abbreviations: AF, amniotic fluid; CS, cesarean section; GA, gestational age; NND, neonatal death; PROM, premature rupture of membranes; TFR, tumor mass to fetal weight ratio; US, ultrasound; * rapidly growing, but no measurements recorded; yr, years; mo, months.

[a]Outcome: average length of follow up for sacrococcygeal teratoma: 92 months.

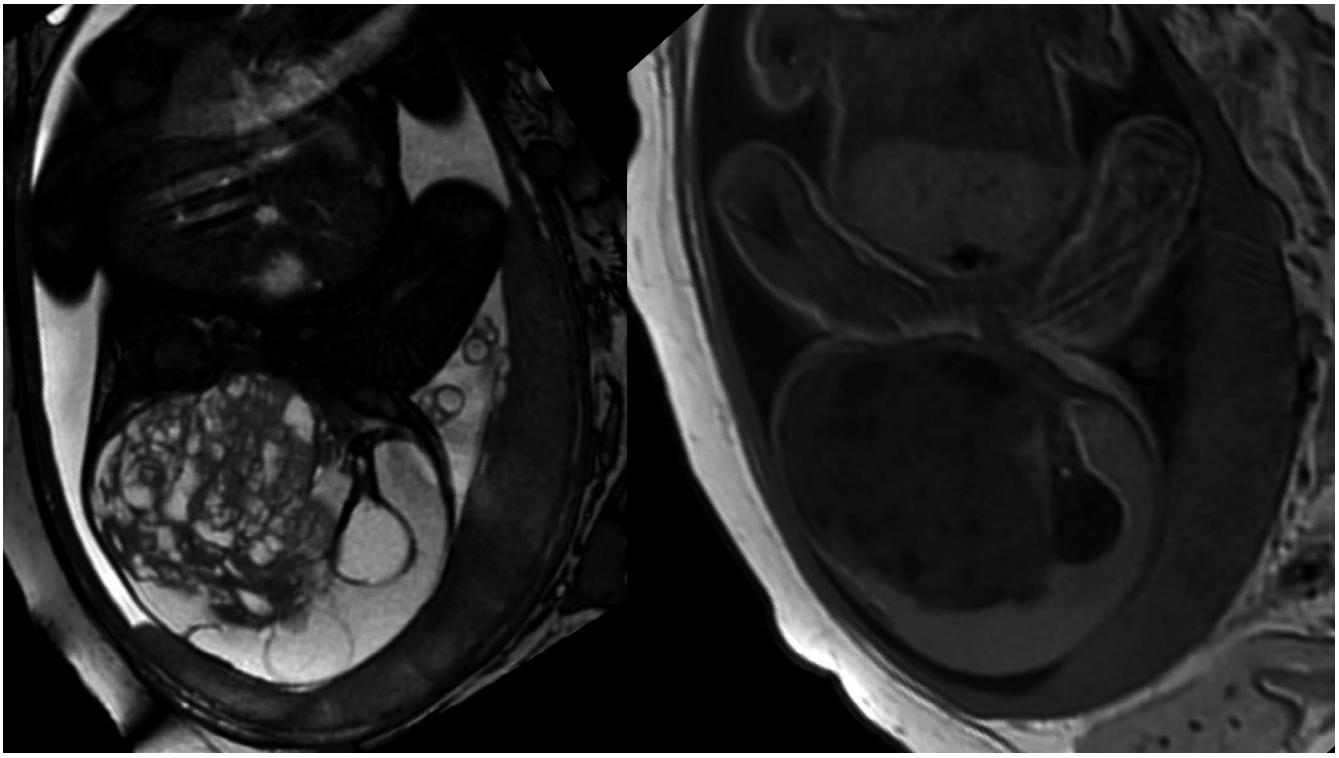

FIGURE 2 Coronal steady state free precession (SSFP) (left image) and T1-weighted sequence (right image) of a sacrococcygeal teratoma (cystic and solid components) in a fetus of gestational age 33^{+2} weeks

gestational weeks by cesarean section including EXIT procedure; one died from cardiac failure 18 hours postpartum. Two children survived: One is tetraplegic with tracheo- and gastrostoma, and a shunt for hydrocephalus, and one suffers from severe hydrocephalus after two cardiac arrests and extracorporeal membrane oxygenation (ECMO) ventilation. Histopathological records were available from 8 of 10 fetuses with non-SCTs, and all were immature teratomas.

Characteristics of 14 fetuses with sonographic suspicion of cardiac RMs are shown in Table 4. In 10/14 fetuses (71%), the RM were associated with TSC. Three fetuses had no evidence of TSC (one with invasive testing in the second trimester and two with genetic testing from umbilical cord blood at delivery). Among the four cases without TSC, one is healthy after spontaneous regression of the tumor after birth, one survived and is healthy after neonatal surgical resection of the RM in the right ventricle, and one received sirolimus, causing partial regression of the RM in the left ventricle/interventricular septum and is symptom-free. One fetus (case 14 in Table 4) presented with an echogenic mass in the right ventricle and atrium and sonographic suspicion of RM. The fetus developed pericardial effusion at 35 weeks and died 8 days postpartum. Autopsy revealed pulmonary artery hypoplasia with a large myocardial fibroma filling the right atrium and ventricle. MRI was performed in 10 of 14 fetuses and neonates (71%); Five cases with TSC had more than one MRI (3 MRIs, n = 3; 2 MRIs, n = 3). Normal cerebral MRI findings despite sonographic suspicion of TSC due to cardiac RM(s) were recorded at gestational age 22-30; the first abnormal cerebral MRI scans were found in week 26 in one case, in all other cases from week 32 onwards up to 3 months postpartum.

Fetal cerebral MRI examinations revealed subependymal nodules which were not detected during targeted central nervous system ultrasonography. Cardiac RM could also be depicted on fetal MRI, when fetal echocardiography showed sonographic evidence of RM. Of the 14 fetuses with cardiac tumors, six (43%) did not survive (five terminations of pregnancy for TSC, one neonatal death with large myocardial fibroma). Among the eight survivors, three are healthy and five have genetically verified tuberous sclerosis.

Thirteen fetuses with lymphatic malformations were observed (Table 5). Two pregnancies were terminated and one child died at 7 months of age after an infection. In two cases, sonography suspected a close correlation between the cervical LM and the trachea, strongly suggesting a possible EXIT procedure, but in both fetuses, prenatal MRI was useful in ruling out airway compression.

Sixteen fetuses with other tumors were observed during the study period. Six fetuses had arterial-venous malformations or hemangiomas: three survived and are healthy, one is neurodevelopmentally retarded, one had spontaneous tumor regression postpartum, and one pregnancy with fetal hemangioma in the posterior fossa was terminated. Three fetuses had other central nervous lesions; one pregnancy with a cystic cortical fetal tumor was terminated. Another fetus with a cystic tumor of >5 cm in the right hemisphere, discovered near term, was delivered shortly after the diagnosis. The cystic tumor corresponded to the remnants of a hemorrhagic-ischemic insult prenatally of unknown etiology; the child survived most severely retarded. A fetus presented at 36 weeks with a solid tumor in the cerebral midline, postpartum

TABLE 3 Tumor characteristics: Teratomas other than sacrococcygeal

Case	GA at presentation, weeks	Tumor location	Initial tumor size, cm^3	US evidence of cardiac compromise	GA at delivery, weeks	Histopathology	Outcome[a]
1	28 1/7	Pericardium	13.7	Hydrops, atrial fibrillation	28 1/7	Immature mediastinal teratoma Grade 3	Healthy at 14 years
2	27 6/7	Pericardium	32.5	Hydrops	28	Immature cystic teratoma	Healthy at 14 months
3	21 3/7	Left half of face, skull base, brain	growing rapidly	no	23	Immature teratoma Grade 3	TOP
4	29 2/7	Neck	21.1	no	30 3/7	Immature teratoma	CS +EXIT, survived/ serious illness[b]
5	21	Neck, thyroid	512	Hydrops, hydramnios	21 1/7	Immature cervical teratoma	TOP
6	31 5/7	Neck	209	Hydramnios	34	Immature teratoma Grade 2	CS +EXIT, survived/ serious illness[c]
7	29 5/7	Neck, thyroid	unknown	Hydramnios	30 4/7	Immature cervical teratoma	CS +EXIT, NND 18 hours[d]
8	36 4/7	Face (upper lip)	111	no	unknown	unknown	TOP
9	18 2/7	Face (upper jaw)	48	no	unknown	unknown	TOP
10	21 2/7	CNS midline	180	no	unknown	Immature teratoma	TOP

Abbreviations: CNS, central nervous system; CS, cesarean section; GA, gestational age; NND, neonatal death; TOP, termination of pregnancy; US, ultrasound; +EXIT, with ex utero intrapartum treatment procedure.

[a]Outcome: average length of follow up for teratomas other than sacrococcygeal: 86 months.

[b]Fetus 4 survived tetraplegic tracheostomy- and gastrostomy-dependent, with shunting for hydrocephalus.

[c]Fetus 6 survived after tumor resection, two cardiopulmonary resuscitations and ECMO ventilation with severe hydrocephalus.

[d]Fetus 7 died 18 hours after delivery from cardiorespiratory insufficiency.

TABLE 4 Clinical features, including number and size of tumors at initial diagnosis, and number of tumors at birth or at termination of pregnancy, of 14 fetuses with ultrasound suspicion of cardiac rhabdomyoma. Abnormal and normal findings at MRI indicate the presence or absence of cerebral lesions related to tuberous sclerosis complex (TSC)

Case	GA (weeks)	Family history	Hydrops	Number of tumors at diagnosis	Number of tumors at birth	Tuberous sclerosis complex (TSC)	Location	Largest diameter(mm)	Initial fetal MRI (weeks/ finding)	Second fetal MRI (weeks/ finding)	Age at first abnormal MRI	Outcome[a]
1	21 6/7	–	–	3	3	TSC1 (pre)	RV	8	22/Normal	—	—	TOP
2	23 1/7	–	–	2	2	TSC2 (pre)	RV	10	—	—	—	TOP
3	26 6/7	–	–	multiple	multiple	TSC (post)	RV + LV	8.5	22/Normal	34/Abnormal	34 weeks	Alive
4	33 0/7	–	–	multiple	multiple	TSC (pre)	RV + LV	9	33/Abnormal	-	33 weeks	TOP
5	20 0/7	–	–	1	1	TSC (pre)	LV	5	22/Normal	32/Abnormal	32 weeks	TOP
6	21 2/7	–	–	1	2	TSC1 (post)	LV	7	23/Normal	30/Normal	3 months pp	Alive
7	21 2/7	–	–	1	1	TSC (post)	IVS	4.5	24/Normal	29/Normal	2 days pp	Alive
8	22 0/7	–	–	1	1	—	IVS	7.7	22/Normal	—	—	Alive
9	22 0/7	–	–	1	1	—	IVS	4	—	—	—	Alive
10	22 2/7	+	+	1	multiple	TSC2 (post)	RV	11	23/Normal	26/Abnormal	26 weeks	Alive
11	23 6/7	–	–	1	1	—	RV	6	—	—	—	Alive
12	27 4/7	+	–	1	1	TSC (post)	RV	6	—	—	3 months pp	Alive
13	29 4/7	–	–	1	1	TSC (pre)	RA	20	32/Abnormal	—	32 weeks	TOP
14	35 4/7	–	+	1	1	—	RV + RA	30	—	—	—	NND[b]

Abbreviations: GA, gestational age; IVS, interventricular septum; LV, left ventricle; MRI, magnetic-resonance imaging; (post), postnatal genetic testing; pp, postpartum; (pre), prenatal genetic testing; RA, right atrium; RV, right ventricle; TOP, termination of pregnancy.

[a]Outcome: average length of follow up for cardiac rhabdomyomas 77 months.

[b]NND, neonatal death (autopsy: myocardial fibroma).

TABLE 5 Lymphatic malformations: Location, findings at prenatal ultrasound and MRI, fetal outcome and postnatal management

Case	Location	GA at initial US diagnosis (weeks)	Initial MRI assessment (weeks)	Maximum diameter whole of lesion(cm; US)	Maximum diameter of largest cyst(cm; MRI)	Solid/ microcystic components(cm; MRI)	Oliver type	Outcome[a]	Postnatal management
1	cervical/ axillary	26 4/7	27 5/7	4.5	4,5	1,5	III/IV	Alive	sclero
2	retroperitoneal	21 6/7	22 6/7	8.9	4,3	-	I	Alive	surgery
3	right half of body	25 3/7	25 3/7	8.0	3,4	-	I	TOP	
4	right lower quadrant	24 4/7	24 4/7	6.4	1,9	-	I	Alive	sclero
5	thorax/axillary	22 6/7	-	5.0	n.d.	n.d.	n.d.	Alive	surgery
6	right upper quadrant	21 4/7	-	n.d.	n.d.	n.d.	n.d.	TOP	
7	thorax	15	21 1/7	16	3,6	-	I	Death/7mo	surgery + sclero
8	cervical	25 4/7	27 1/7	7.2	1,7	3,4	IV	Alive	sclero
9	thorax	21 2/7	24 3/7	7.5	2,6	-	I	Alive	surgery + sclero
10	axillary	26 6/7	26 6/7	7.4	3,8	-	I	Alive	surgery
11	right upper quadrant	26	27 3/7	4.0	2,7	-	I	Alive	surgery
12	thorax/axillary	26 4/7	27 6/7	6.9	2,5	-	I	Alive	surgery
13	left leg	20	21 3/7	8.1	2,0	-	I	Alive	sclero

Abbreviations: GA, gestational age; n.d., not determined; sclero, sclerotherapy; TOP, termination of pregnancy.

[a]Outcome: average length of follow up for lymphatic malformations 46 months

imaging revealed a large calcified lipoma of the corpus callosum. The child shows normal development at age 2 years.

Two fetuses with an adrenal lesion presented at 36 and 38 weeks, respectively. Whereas the two cystic lesions had similar sonographic appearances, sonography in one neonate at 6 weeks was normal, which supported the diagnosis of the cystic lesion as being remnants after adrenal bleeding. Fetal MRI showed a hemorrhagic cystic mass cranial to the left upper renal pole. The other child is currently undergoing chemotherapy for a cystic adrenal neuroblastoma. In this case the prenatal MRI also showed a multicystic mass with solid parts attached to the cranial right renal pole. Three fetuses had hepatic tumors. One fetus with an av-malformation within the left liver lobe is developing normally, but is under pediatric surveillance for chronic anemia and elevated liver enzymes. Of the two fetuses with hepatoblastoma, one died 6 weeks postpartum and one child is undergoing chemotherapy.

4 | DISCUSSION

We aimed in this study to evaluate morbidity and mortality in fetuses with prenatally diagnosed tumors and to analyze which imaging approaches were most valuable in prediction of long-term outcome. Of the children who suffered fetal tumors, 66% survived. More than half of the children were cured but up to 30% suffered long-term consequences of their disease.

In terms of fetal imaging, we found that MRI was superior to ultrasound both in predicting tumor morphology in teratomas and in delivery planning in cases with head and neck tumors. One-fifth of parents decided to terminate their pregnancy, which received ethical approval at our institution. Following prenatal suspicion of a lesion by ultrasonography and verification by fetal magnetic imaging, parents are usually offered a multidisciplinary approach to allow them to make a fully informed consent to choose to continue or terminate the pregnancy. Bearing in mind the improvement of surgical and medical facilities in recent years, future data analyses might show a smaller percentage of parents who sought to terminate their pregnancy.

SCTs are the most common fetal tumors, carrying a variable prognosis.[4,6,7,9,21] Tumor-fetal ratio and hydrops have been advocated to predict outcome[2,3,18] but were not useful predictors for outcome in our series. Early delivery and fetal surgery have been suggested to improve prognosis.[5] MRI is widely used in these fetuses, but its role is unclear.[1,4,21] More data are needed to support this finding but preliminary results from our series suggest that there is a high correlation between fetal MRI findings, outcome and histopathology in SCTs. MRI was also helpful in delineating the surrounding head and brain structures in teratomas other than SCT, as previously described.[22-24] Three pregnancies had an EXIT procedure between weeks 30 and 34, and outcome was poor in all of them.

Poor outcome of fetuses with RM has been associated with a cardiac tumor size of 20 mm or more, number of lesions, dysrhythmia, hydrops and family history of TSC.[25-27] The association between RM and TSC was also strong in our series, with >70% of fetuses affected, regardless of the number or size of cardiac tumors. Dysrhythmia was never observed; of the two hydropic fetuses, one survived with TSC, and one with a large fibroma of the right heart died neonatally. In fetuses with RM, we evaluated at which stage of pregnancy signs of cerebral TSC might be visible in MRI, when directly looked for. Reports on prenatal MRI in fetuses with TSC are scarce.[25] MRI, however, was not helpful for early diagnosis of TSC: Seven fetuses had early targeted MRI before 25 gestational weeks, of which six (86%) had verified TSC; all were negative at initial cerebral MRI. Further fetal and neonatal cerebral MRI showed subependymal nodules. This finding may be significant for parent counseling, as early MRI does not provide a full-blown picture of the disease.

Prognosis of fetal lymphatic malformation has been related to lesion size, cystic and solid components, and presence of septations.[20,26,28-31] In the 13 cases presented, we found no association whatsoever between location, lesion size or classification [20] and outcome. MRI was helpful in delivery planning in avoiding an unnecessary EXIT procedure, as well as for the differential diagnosis from other cystic lesions.

The relatively large number of cases of prenatally diagnosed fetal tumors with long-term outcome data renders this study valuable. The monocenter study design and continuity of staff in all three departments limits the risk of interrater variability and guarantees high-quality fetal assessment over a long observational period. Our study, however, is not devoid of limitations, first and foremost due to its retrospective study design, with important information missing in those cases that we had to exclude. Furthermore, we acknowledge that over time, advances in prenatal imaging techniques and the improvements in diagnosis of fetal malformation limit the generalizability of our data.

To the best of our knowledge, very limited data on long-term outcome after fetal and/or neonatal therapy for fetal tumor patients are available. Factors that predict prognosis of fetal tumors are of utmost significance for antenatal management, parent counseling and planning of delivery and postpartum care.

On the basis of the results from this study, we have implemented uniform MRI assessment for fetal teratomas, with risk stratification according mainly to MRI rating of maturity in SCTs. Fetal cardiac tumors do not profit from early MRI before 25 weeks of gestation to predict TSC, which is solely the domain of genetic testing. The extent and severity of cerebral involvement of fetuses with TSC can, however, be evident on fetal MRI after 30 weeks. If early delivery is considered for fetal tumor patients, the question remains as to the best timing, balancing the odds of intrauterine decompensation against sequelae of extreme prematurity. All decisions regarding best approach rely on the value of different imaging and surveillance protocols. Parent counseling as well as medical multidisciplinary decision-making need to address clearly which outcome is considered in high-risk fetal tumor patients.

5 | CONCLUSION

The rate of survivors with serious long-term illness among fetuses with prenatal diagnosis of a tumor was high. MRI is specifically

helpful for risk stratification in fetal teratomas and delivery planning in head and neck tumors.

CONFLICT OF INTEREST

None.

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How to cite this article: Ulm B, Muin D, Scharrer A, Prayer D, Dovjak G, Kasprian G. Prenatal ultrasound and magnetic resonance evaluation and fetal outcome in high-risk fetal tumors: A retrospective single-center cohort study over 20 years. *Acta Obstet Gynecol Scand*. 2020;99:1534–1545. https://doi.org/10.1111/aogs.13933