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Ⅲ.　研究成果の刊行物・別刷

Journal of Pediatric Surgery (2012) 47, 441–447

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Journal of Pediatric Surgery

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Original articles

Outcomes of prenatally diagnosed sacrococcygeal teratomas: the results of a Japanese nationwide survey

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Received 4 June 2011; revised 28 July 2011; accepted 27 August 2011

Key words:
Prenatal diagnosis;
Sacrococcygeal teratoma;
Tumor component;
Preterm labor;
Multicenter survey;
Mortality

Abstract

Background/Purpose: Few large multicenter surveys have been performed on sacrococcygeal teratomas (SCTs) describing both the prenatal and postnatal courses. The aim of this study was to review and report on the prenatal surveillance and postnatal outcome of a large cohort of fetuses with SCTs in Japan.

Methods: A nationwide retrospective cohort study was conducted on 97 fetuses prenatally diagnosed with SCTs between 2000 and 2009. The prenatal course, perinatal data, and postnatal outcome were reviewed.

Results: Eleven pregnancies were terminated before 22 weeks of gestation. Of the 86 remaining fetuses, 3 died in utero, and 83 were delivered. Three infants died before surgery, and 8 infants died after excisional surgery. The overall mortality was 26%, with a mortality excluding terminations of 16%. The gestational age at delivery was younger than 28 weeks in 5, 28 to 31 weeks in 13, 32 to 36 weeks in 27, and 37 weeks or more in 37 cases, with mortality rates of 60%, 38%, 11%, and 0%, respectively. The tumor component was predominantly cystic in 54 and predominantly solid in 32 cases, with mortality rates of 2% and 33%, respectively.

Conclusions: The overall mortality of prenatally diagnosed SCTs excluding terminations was 16%. Early delivery and predominantly solid component tumors were associated with an increased risk of mortality.

Sacrococcygeal teratoma (SCT), which originates from the 3 germinal layers, is the most common congenital tumor, with a birth prevalence of 1 in 27,000 live births [1]. Sacrococcygeal teratomas diagnosed postnatally have been associated with an excellent prognosis after surgical excision [2-5]. In contrast, it has been reported that fetuses with a prenatally diagnosed SCTs still have a high risk of death even if the prenatal diagnosis may have made a contribution to improvement of the outcome [6]. The main reason for the

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0022-3468/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.jpedsurg.2011.08.020

poor prognosis in fetal SCTs is high-output cardiac failure caused by increased blood flow according to the amount of solid component present in the tumor [7,8] and rupture of the tumor during delivery with a massive hemorrhage [9,10]. However, the reported mortality rate excluding terminations in the fetuses with SCTs varied widely from 18% to 63% in different series [6-16]. Most of these studies were conducted in a single institution with a small number of patients, and there may have been selection bias [8] because some of the institutions were specialized centers for fetal treatment. The natural history of fetal SCTs has not been fully characterized because few large multicenter surveys have been performed describing both the prenatal and postnatal courses. The aim of this study was to review and report on the prenatal surveillance and postnatal outcome of a large cohort of fetuses with SCTs in Japan based on a nationwide survey.

1. Materials and methods

A nationwide retrospective cohort study was conducted on fetuses prenatally diagnosed with SCTs at major Japanese perinatal centers. We initially sent a preliminary questionnaire requesting the number of fetuses prenatally diagnosed with SCTs between January 2000 and December 2009 to 325 major perinatal centers in Japan and asked them to participate in our detailed survey. One-hundred ninety centers (58.5%) responded to the preliminary survey and reported that there were 138 cases with SCTs diagnosed prenatally during the past 10 years. We then sent a second form requesting further details about the fetuses from the centers that had corresponding cases and had accepted our offer to participate in a detailed survey. Forty-eight centers that had 101 cases of fetal SCTs consented to participate in our survey and returned the forms with further details. Four fetuses that had not been followed up until fetal demise or live birth owing to maternal transfer were excluded from the study, so 97 fetuses prenatally diagnosed with SCTs between January 2000 and December 2009 at 46 Japanese perinatal centers were included in the study and analyzed. The patient demographics, including the year of prenatal diagnosis, gestational age at diagnosis, occurrence of polyhydramnios, signs of hydrops fetalis, fetal interventions, prenatal outcome, mode of delivery, gestational age at delivery, sex of the fetus, and birth weight were reviewed. The type of the tumor component, tumor location, histology of the tumor, maximum diameter of the tumor, and postnatal outcome were also reviewed.

Polyhydramnios was regarded as positive if there was a finding of polyhydramnios either in the initial or final fetal ultrasonography. The presence of signs for hydrops fetalis was defined as positive if there was a finding of ascites, pleural effusion, or skin edema either in the initial or final fetal ultrasonography. The type of the tumor component was defined as 1 of 4 categories, such as cystic type (>90% of the tumor is cystic), predominantly cystic mixed type (50%-90% of the tumor is cystic), predominantly solid mixed type (50%-90% of the tumor is solid), and solid type (>90% of the tumor is solid), and the cases were classified according to the schema described in the questionnaire (Fig. 1). The type of the tumor component was determined by pathologic findings in surgical cases and by prenatal or postnatal diagnostic imaging in nonsurgical cases. The tumor location was categorized according to Altman's classification [2] determined by operative findings or diagnostic imaging. The maximum diameter of the tumor was defined as the maximum value of the maximum diameter of the resected tumor, the maximum diameter of the computed tomography performed after birth, and the maximum diameter of the magnetic resonance imaging performed after birth in the cases of live births and as the maximum value on fetal ultrasonography in cases of fetal demise.

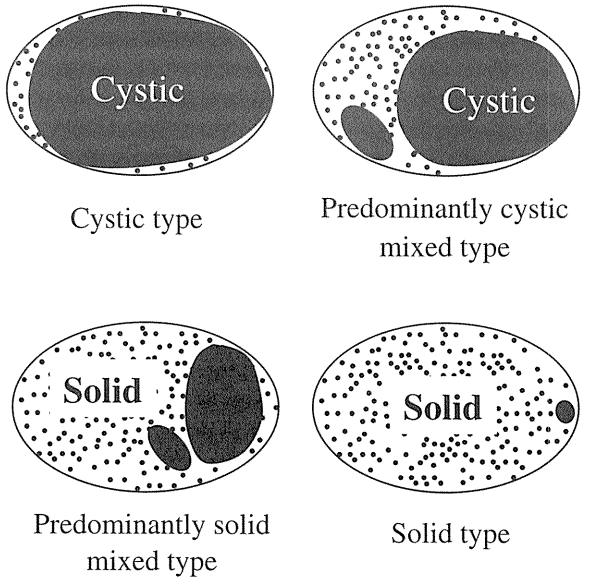

Fig. 1 A schematic diagram of the types of tumor components. Cystic type, more than 90% of the tumor is cystic; predominantly cystic mixed type, 50% to 90% of the tumor is cystic; predominantly solid mixed type, 50% to 90% of the tumor is solid; solid type, more than 90% of the tumor is solid.

The data were expressed as the medians (range). The frequencies and percentages were used to describe categorical data. The χ^2 test was used for the analysis of categorical data. $P < .05$ was considered to indicate statistical significance. Statistical analyses were performed with the JMP software program (version 8.02; SAS Institute, Inc, Cary, NC). This retrospective survey was approved by the institutional review boards of the 5 participating institutions (institutional review board approval no. 09392, National Center for Child Health and Development).

2. Results

The annual number of the fetuses with SCTs was less than 7 before 2005 but increased thereafter and exceeded 14 cases

per year after 2007 (Fig. 2). The median maternal age was 30 years (range, 18-41 years), and median gestational age at diagnosis was 25 weeks of gestation (range, 15-36 weeks). Twenty-four cases (24.7%) were diagnosed before 22 weeks of gestation, the period in which a termination of pregnancy is legally permitted in Japan [17]. Eleven pregnancies were terminated before 22 weeks of gestation, and 86 cases intended to deliver (Fig. 3). Of the 24 cases diagnosed before 22 weeks of gestation, there were no significant differences in the size of the tumor, type of the tumor component, or incidence of the signs for hydrops fetalis between the cases that were terminated and the cases that were intended to be delivered (data are not shown).

The outcomes of the infants with prenatally diagnosed SCTs are shown in Fig. 4. Of the 86 nonterminated fetuses, 3 resulted in intrauterine fetal deaths, and 83 survived to be born. Of these survivors, 4 cases underwent fetal intervention, including radiofrequency ablation (n = 1), abdominal paracentesis (n = 1), and cyst aspiration (n = 2). All 4 of these cases underwent tumor resection, and 3 survived after the surgery. The patient who underwent paracentesis died of a massive hemorrhage during the surgery. Amnioreduction had been performed in 11 pregnancies to prevent preterm labor and maternal discomfort owing to polyhydramnios. After the live birth, 3 infants died before surgery on the day of birth, and 80 infants underwent excisional surgery at a median of 74 hours (range, 1-1581 hours). Twenty-five infants underwent surgery in the first 24 hours of life, and 6 of them (24%) died, whereas 55 cases underwent surgery after 24 hours, and only 2 (4%) of them died. Four infants died after surgery during the early neonatal period, 2 died during the later neonatal period, and 2 died later in infancy. Of the 9 neonatal deaths, 7 were related to massive hemorrhage from the tumors. Bleeding from the tumors was already recognized in 6 neonates at the time of cesarean section delivery, and 4 of them, including 2 neonates with a tumor that ruptured during the delivery, died on the day of birth. The median follow-up of survivors was 23 months (range, 0-113 months). The overall mortality was 26% (25/97), with a mortality excluding terminations of 16% (14/86).

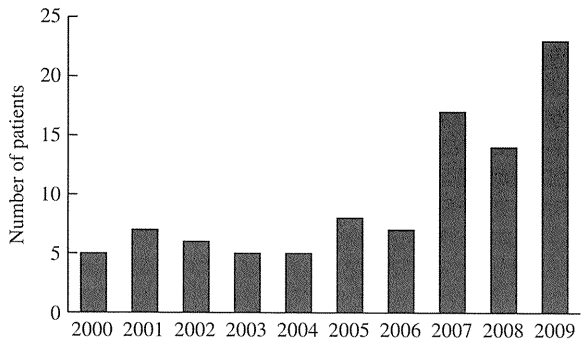

Fig. 2 The number of the fetuses with a prenatal diagnosis of SCT.

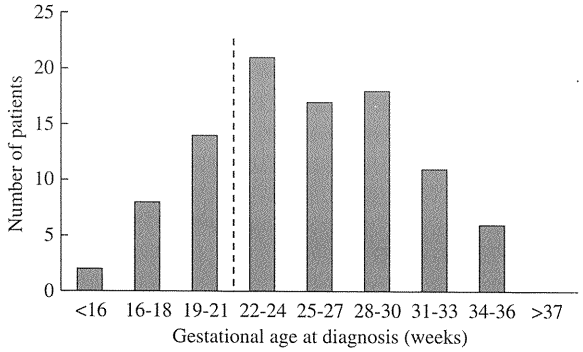

Fig. 3 The distribution of the gestational age at diagnosis. A termination of pregnancy is legally permitted in Japan before 22 weeks of gestation (broken line).

Table 1 reviews the demographics and mortality of the fetuses with SCTs that were intended to be delivered. The fetuses that had been diagnosed before 28 weeks of gestation had a significantly higher mortality rate compared with those diagnosed after 28 weeks of gestation. They were delivered at a median gestational age of 36.4 weeks (range, 26-41 weeks). Forty-five fetuses (55%) were born prematurely, and

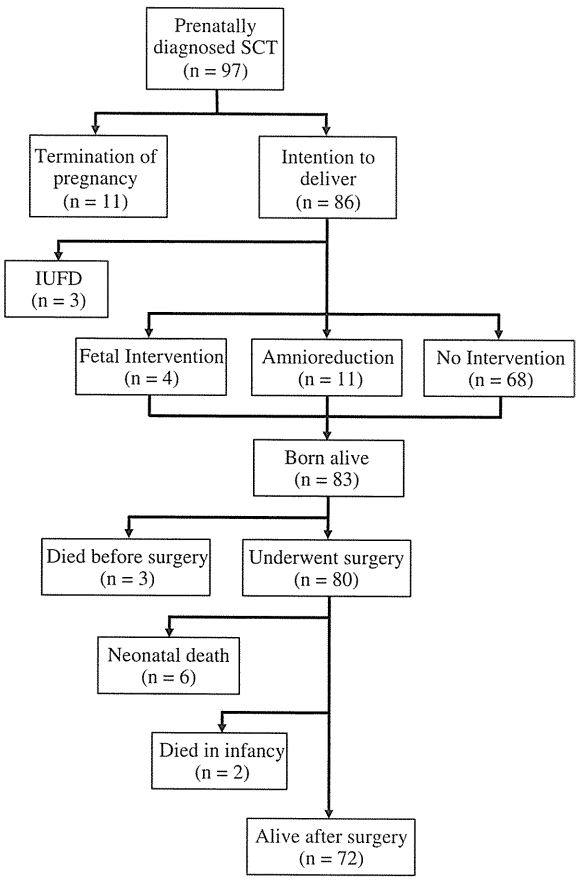

Fig. 4 The outcomes of prenatally diagnosed SCT (2000-2009). IUFD indicates intrauterine fetal death.

Table 1 Demographics and mortality of the fetuses that were intended to be delivered after a prenatally diagnosis of SCT

Characteristics	Distribution of patients (%)	Mortality (%) and *P* value
Gestational age at diagnosis (wk)	n = 86	*P* = .020
<22	13 (15.1)	3 (23.1)
22-27	38 (44.2)	10 (26.3)
≥28	35 (44.2)	1 (2.9)
Gestational age at delivery (wk)	n = 82	*P* < .001
<28	5 (6.1)	3 (60.0)
28-31	13 (15.9)	5 (38.5)
32-36	27 (32.9)	3 (11.1)
≥37	37 (45.1)	0 (0.0)
Sex	n = 85	*P* = .303
Male	23 (27.1)	2 (8.7)
Female	62 (72.9)	11 (17.7)
Birth weight (g)	n = 82	*P* = .404
<2000	7 (8.5)	1 (14.3)
2000-2999	42 (51.2)	8 (19.0)
3000-3999	27 (32.9)	2 (7.4)
≥4000	6 (7.3)	0 (0.0)
Mode of delivery	n = 82	*P* = .036
Vaginal delivery	12 (14.6)	1 (8.3)
Planned cesarean section delivery	39 (47.6)	2 (5.1)
Emergency cesarean section delivery	31 (37.8)	8 (25.8)

37 fetuses (45%) were delivered at full term. The mortality rates based on age at delivery were significantly different, and the younger infants demonstrated a higher mortality rate. The male-to-female ratio was 1:2.6. The median birth weight was 2893 g (range, 1020-5014 g). There was no significant difference in the mortality among the infants with different

Table 2 Characteristics of fetal ultrasonography and the tumor findings of the fetuses that were intended to be delivered along with their mortality

Characteristics	Distribution of patients (%)	Mortality (%) and *P* value
Polyhydramnios	n = 86	*P* = .078
Yes	26 (30.2)	7 (26.9)
No	60 (69.8)	7 (11.7)
Sign of hydrops fetalis	n = 86	*P* < .001
Yes	14 (16.3)	8 (57.1)
No	72 (83.7)	6 (8.3)
Altman's classification	n = 84	*P* = .734
I	48 (57.1)	10 (20.8)
II	26 (31.0)	3 (11.5)
III	5 (5.9)	0 (0.0)
IV	5 (5.9)	1 (20.0)
Type of tumor component	n = 86	*P* < .001
Cystic type	23 (26.7)	0 (0.0)
Predominantly cystic mixed type	31 (36.0)	2 (6.4)
Predominantly solid mixed type	25 (29.1)	8 (32.0)
Solid type	7 (8.1)	4 (57.1)
Maximum diameter of the tumor (cm)	n = 86	*P* = .213
<5.0	4 (4.7)	0 (0.0)
5.0-9.9	26 (30.2)	0 (0.0)
10.0-14.9	28 (32.6)	7 (25.0)
15.0-19.9	22 (25.6)	5 (22.7)
≥20.0	6 (7.0)	2 (33.0)

birth weights. Twelve fetuses (15%), including 2 cases who had undergone cyst aspiration for decompression before delivery, were born by vaginal delivery, whereas 70 fetuses (85%) were born via cesarean delivery: 31 because of the tumor size, 10 because of fetal cardiac failure, 9 because of the repetitive cesarean section, 5 because of the fetal distress, and 15 for other reasons. None of the fetuses delivered by cesarean section underwent ex utero intrapartum therapy (EXIT). The fetuses delivered by emergency cesarean section demonstrated a significantly higher mortality rate. Associated anomalies were detected in 10 (12%) of 83 infants and included congenital heart disease (n = 5), undescended testes (n = 2), an anorectal anomaly (n = 1), an ectopic ureter (n = 1), hydrocephalus (n = 1), and intestinal duplication (n = 1).

Table 2 reviews the characteristics of the fetal ultrasonography and the tumor findings in the fetuses that were intended to be delivered along with their mortality. Polyhydramnios was recognized in 30% of the patients, and some signs for hydrops fetalis were seen in 16% of the cases. The mortality of the fetuses with 1 sign of hydrops fetalis was higher than that of the fetuses without any sign of hydrops fetalis. Type I Altman's classification was the most common tumor location, and type II was the second most common. There were no statistically significant differences in the mortality rates among the infants with different Altman's classifications. The type of the tumor component was predominantly cystic (>50% cystic) in 54 cases (63%) and predominantly solid (>50% solid) in 32 cases (37%). There were significant differences in the mortality among the patients with different types of the tumor components, and the predominantly solid type was associated with higher mortality. Although there was no statistically significant difference in the mortality among the patients with different maximum diameters of the tumor, no fetuses that had a tumor with a maximum diameter less than 10 cm by any measurements died.

3. Discussion

We reviewed the prenatal course, perinatal data, and postnatal outcome in this Japanese nationwide retrospective cohort study conducted on 97 fetuses prenatally diagnosed with SCTs between 2000 and 2009. Of the 97 fetuses, 11 pregnancies were terminated, 3 died in utero, and 11 infants died after live births. The overall mortality including the termination of pregnancy was 26% (25/97), and the mortality excluding such terminations was 16% (14/86). The perinatal mortality and the neonatal mortality of this cohort were 12% (10/86) and 11% (9/83), respectively. Table 3 includes data from published series of fetal SCTs involving 10 or more cases, including our present results, which are the largest retrospective cohort study conducted for fetuses with a prenatal diagnosis of SCT [6-16]. Although the mortality among fetuses with SCT varied widely in different series, the outcome of the present study was better than that reported previously [6-11,14-16]. One of the reasons for this discrepancy is the advances that have been made in maternal or fetal management and perinatal care in recent years, as cases from more 10 years ago were included in some series. The other reason may be the effects of selection bias in some institutions, as some of them were highly specialized centers for fetal intervention and may be more likely to receive referrals of more serious cases associated with higher mortality.

Another possibility is that there was an increased population with a prenatal diagnosis of SCTs in our country likely owing to the advent of improved antenatal imaging techniques and screening. The Japanese Society of Pediatric Surgeons reported in their neonatal surgical survey performed every 5 years that the ratio of prenatal diagnosis in neonates with SCTs was 44% in 2003 [18] and 82% in 2008 [19]. The number of registered cases has increased rapidly in the past few years along with the increase in the ratio of prenatal diagnosis during the 5-year period from 2003 to 2008 (Fig. 2). Improvements in prenatal diagnosis may have

Table 3 The number of the patients and the outcomes reported in previous studies

Author	Study period	Study design	No. of cases	No. of TOP	IUFD	Postnatal death	Mortality excluding TOP (%)
Bond et al [7]	1990	M	45	11	11	6	17/34 (50%)
Sheth et al [11]	NA	M	15	2	5	2	7/13 (54%)
Holterman et al [10]	1980-1997	S	24	3	4	5	9/21 (43%)
Brace et al [9]	1992-1998	S	10	2	2	3	5/8 (63%)
Westerburg et al [8]	1986-1998	S	17	2	0	6	6/15 (40%)
Kamata et al [12]	1979-1999	S	14	0	1	2	3/14 (21%)
Hedrick et al [6]	1995-2002	S	30	4	5	7	12/26 (46%)
Benachi et al [13]	1983-2003	M	44	4	2	5	7/40 (18%)
Makin et al [14]	1993-2004	S	35	6	3	4	7/29 (24%)
Sy et al [15]	1991-2005	S	27	3	5	3	8/24 (33%)
Wilson et al [16]	2003-2006	S	23	4	3	4	7/19 (37%)
Present study	2000-2009	M	97	11	3	11	14/86 (16%)

NA indicates not available; S, single-institutional study; M, multicenter study; TOP, termination of pregnancy; IUFD, intrauterine fetal death.

contributed to the increased detection of milder cases that would not have been diagnosed previously. Although there were no significant differences in the prognostic factors between the 11 terminated cases and the 13 continued pregnancies for fetuses that were diagnosed before 22 weeks of gestation, termination of pregnancy may have contributed to the improvement of the mortality because the cases with earlier presentation demonstrated poorer prognosis, probably because of the larger tumor growth, compared with the cases with later presentation [8,16] (Table 1).

This is the first Japanese multicenter survey conducted for fetuses with a prenatal diagnosis of SCT. Our preliminary survey revealed that there were at least 138 fetuses with SCT during the past 10 years in Japan, and 70% of them were surveyed in detail. The population survey report of the Ministry of Health, Labour and Welfare of Japan reported that there were 11,155,608 live births and 329,757 stillbirths during the period between January 2000 and December 2009. Judging from the birth prevalence of SCT, the number of patients with SCT predicted for this period was estimated to be approximately 400 cases including postneonatally presented cases, and the patient number in our survey therefore corresponded to approximately one fourth of the estimated cases for that period. The Japanese Society of Pediatric Surgeons reported that 16 neonates with prenatally diagnosed SCTs were treated in 2003 [18], and 23 neonates with prenatally diagnosed SCTs were treated in 2008 [19]. Together with this demographic information, it is estimated that about half of the prenatally diagnosed cases of SCT in our country have been collected and surveyed from the 46 perinatal centers participated in the present study. In consequence, the results of this study accurately describe the current status of both the prenatal and postnatal courses of these infants and characterize the natural history of fetal SCTs in our country. This study will therefore provide useful information for prenatal counseling of parents.

The gestational age of the fetus at delivery had a major impact on the perinatal and postnatal mortality, as has been previously reported [6,9,10,16]. The mortality rates based on age at delivery were significantly different, and the younger infants demonstrated a higher mortality. This was presumably because of the synergistic effects of several factors, including the high mortality owing to prematurity, the high risk of preterm labor owing to the high-output cardiac failure and polyhydramnios, and the large tumor size that required early delivery. With regard to the mode of delivery, our data showed that emergency cesarean section was likely to be selected in the high-risk patients. The well-known Altman's classification into 4 types, depending on the relationship of the extrapelvic and intrapelvic parts, demonstrated no correlation with the outcome. In contrast, the type of the tumor component was well correlated with the outcome, which is consistent with the previous reports [6,8,10,13]. The solid component of the SCT is generally very vascular and has the potential for rapid growth, resulting in an increased risk of high-output cardiac failure and massive hemorrhage [6,13,15].

Although there were no statistically significant differences in the mortality rates among the cases with different maximum diameters of the tumors, no fetuses whose maximum diameter was less than 10 cm died. A recent study, which proposed a prognostic classification for the fetuses prenatally diagnosed to have SCT [13], defined 3 risk groups as follows: group A with tumor diameters less than 10 cm, absent or mild vascularity, and slow growth; group B with tumor diameter of 10 cm or greater, pronounced vascularity or high-output cardiac failure, and rapid growth; and group C with a tumor diameter of 10 cm or greater, predominantly cystic lesions with absent or mild vascularity, and slow growth. According to their prognostic classification, our cases were classified into 30 cases of group A, 28 cases of group B and 28 cases of group C, with mortality rates of 0%, 39%, and 11% respectively.

There have been some report of fetal interventions, such as maternal-fetal surgery to resect the tumors [6,14], radiofrequency ablation [20], major vessel laser ablation [14], and vessel alcohol sclerosis [14], to prevent the high-output cardiac failure. In some cases, there were indications for prenatal intervention, such as amniodrainage, to prevent preterm labor [6,14,16] and cyst decompression before delivery to prevent tumor rupture [6,9,14,16]. There were 4 cases of fetal intervention and 11 cases of amniodrainage in the present study, and all of the cases survived to be born, and 3 cases of fetal intervention and 7 cases of amniodrainage survived to discharge. However, detailed validation may be necessary to evaluate and definitively conclude the efficacy of these prenatal interventions. Of the 9 neonatal deaths, 6 infants had already developed hemorrhage from the tumor at the time of cesarean section, including 2 cases of tumor rupture during the cesarean delivery. Most of them were premature infants who had huge and predominantly solid tumors. An early delivery with an EXIT-to-resection strategy [21] or emergency preoperative tumor embolization [22] may have some benefits for such critical cases.

A major limitation of this study is that this survey was conducted in a retrospective manner by using a questionnaire requesting details about the patients. Many of the centers had a small number of cases, and the maternal and fetal management, including the criteria for fetal intervention, were determined according to the clinical decisions of each institution. Moreover, prognostic factors were analyzed only by a descriptive study. A more detailed analysis of the data and a prospective study will therefore be needed to establish a comprehensive treatment strategy, including preoperative tumor embolization, EXIT procedures, and fetal interventions.

Acknowledgments

This work was supported by a grant from The Ministry of Health, Labour and Welfare of Japan (H22-Nanchi-Ippan-158, Health and Labour Sciences Research Grants for

Research on intractable diseases). The perinatal centers that participated in this survey were Akita University Hospital (Akita), Chiba University Hospital (Chiba), Dokkyo Medical University Hospital (Mibu), Fuji City General Hospital (Fuji), Fujita Health University Hospital (Toyoake), Fukuoka University Hospital (Fukuoka), Gunma Children's Medical Center (Shibukawa), Hiroshima City Hospital (Hiroshima), Hiroshima University Hospital (Hiroshima), Hyogo Prefectural Kobe Children's Hospital (Kobe), Japanese Red Cross Medical Center (Tokyo), Jichi Medical University Hospital (Shimotsuke), Kagoshima City Hospital (Kagoshima), Kameda Medical Center (Kamogawa), Keio University Hospital (Tokyo), Kimitsu Chuo Hospital (Kisarazu), Kitasato University Hospital (Sagamihara), Kobe University Hospital (Kobe), Kochi Health Sciences Center (Kochi), Kumamoto City Hospital (Kumamoto), Kumamoto University Hospital (Kumamoto), Kyorin University Hospital (Mitaka), Kyushu University Hospital (Fukuoka), Matsue Red Cross Hospital (Matsue), Mie University Hospital (Tsu), Miyagi Children's Hospital (Sendai), Nagara Medical Center (Gifu), Nagasaki University Hospital (Nagasaki), Nara Medical University Hospital (Kashihara), National Center for Child Health and Development (Tokyo), National Kyushu Medical Center (Fukuoka), Niigata University Medical and Dental Hospital (Niigata), Ohtawara Red Cross Hospital (Ohtawara), Okayama Medical Center (Okayama), Oita Prefectural Hospital (Oita), Okinawa Prefectural Chubu Hospital (Uruma), Osaka Medical Center and Research Institute for Maternal and Child Health (Izumi), Osaka University Hospital (Suita), Saga University Hospital (Saga), Shizuoka Children's Hospital (Shizuoka), Showa University Hospital (Tokyo), St Marianna University School of Medicine Hospital (Kawasaki), The University of Tokyo Hospital (Tokyo), Toho University Omori Medical Center (Tokyo), Tokyo Womens Medical University Yachiyo Medical Center (Yachiyo), Yamagata University Hospital (Yamagata), Yamanashi Prefectural Central Hospital (Kofu), and Wakayama Medical University Hospital (Wakayama). The authors thank Ms Seimiya of National Center for Child Health and Development and Ms Masumoto, Mr Tamura, and Mr Kurimoto of Japan Clinical Support Unit for their help in processing the data.

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