Evaluating the tumor characteristics according to the histology, the immature teratomas were significantly larger in size at delivery and were associated with a more rapid growth rate than the mature teratomas. Approximately 60 % of the mature teratomas contained cystic or predominantly cystic mixed components, whereas approximately 60 % of the immature teratomas contained solid or predominantly solid mixed components. The preoperative serum level of AFP was significantly higher in the immature teratoma patients (2,81,387 ± 40,664 ng/ml) than in the mature teratoma patients (1,41,487 ± 32,439 ng/ml).

Regarding the perinatal data, the maternal age (27.8 ± 0.73 years old) of the immature teratoma patients was lower than that of the mature teratoma patients (31.0 ± 0.59 years old). The mothers of the patients with immature teratomas experienced perinatal complications more frequently than those of the patients with mature teratomas. The patients with immature teratomas were delivered significantly earlier than those with mature teratomas [median gestational age at delivery; immature teratomas: 32.4 weeks (range 22.7–38.8), mature teratomas: 37.1 weeks (range 22.2–41.0), $P < 0.0001$]. With respect to the mode of delivery, emergent cesarean section was performed in more than 50 % of the cases of patients with immature teratomas, whereas vaginal delivery and planned cesarean section were selected in 3/4 of the cases of patients with mature teratomas.

Regarding the condition of the patient after delivery, the Apgar scores at 1 and 5 min were significantly lower in the patients with immature teratomas than in those with mature teratomas. The serum hemoglobin levels immediately after delivery were significantly lower in the patients with immature teratomas than those observed in the patients with mature teratomas. Rupture of the tumor capsule and bleeding from the tumor was more frequently observed in the cases of immature teratomas than in the cases of mature teratomas. Moreover, subcutaneous edema, disseminated intravascular coagulopathy (DIC), the need for mechanical ventilation and the administration of catecholamines or blood transfusions were more frequently observed in the patients with immature teratomas than in those with mature teratomas.

With respect to the patient's perioperative condition, the preoperative serum hemoglobin levels were significantly lower in the patients with immature teratomas than in those with mature teratomas. The preoperative platelet counts were significantly lower in the patients with immature teratomas than in those with mature teratomas. The amount of blood loss during surgery in the cases of immature teratomas was significantly larger than that observed in the cases of mature teratomas. Blood transfusions were required in approximately 90 % of the cases of immature teratomas and approximately 30 % of the cases of mature teratomas. Cardiac resuscitation was required in 25 % of the patients with immature teratomas and in only one patient with a mature teratoma.

Postoperative DIC, intracranial hemorrhage and disturbance of the lower limbs were observed more frequently in the patients with immature teratomas than in those with mature teratomas. Immature teratomas were associated with a significantly higher mortality rate (number of patients who died at delivery/number of patients who were delivered alive; immature teratomas: 8/31, mature teratomas: 2/48, $P < 0.05$) (Tables 1, 2).

Late recurrence

Among the 72 patients who were discharged alive without tumors, late recurrence was observed in six cases (8.3 %). The clinical features of these six cases are shown in Table 3. There were three boys and three girls.

With respect to the clinical features observed during the neonatal period, the gestational age at delivery ranged between 33 and 41 weeks. There were two type I tumors, one type II tumor and three type III tumors according to Altman's classification. Cystic tumors were observed in

Table 1 Univariate analysis of continuous variables data of tumor histology

Characteristics	Mature teratoma	Immature teratoma	*P* value
Maternal age (years)	31.0 ± 0.59	27.8 ± 0.73	0.001
Gestational age at delivery (days)	253.7 ± 3.9	224.2 ± 4.8	<0.0001
Tumor growth rate (cm/w)	0.46 ± 0.08	0.91 ± 0.10	0.0012
Maximum diameter of the tumor (cm)	11.0 ± 0.73	14.0 ± 0.91	0.0101
Apgar score at 1 min	7.6 ± 0.4	4.8 ± 0.4	<0.0001
Apgar score at 5 min	8.6 ± 0.3	6.8 ± 0.4	0.0002
Hemoglobin at delivery (g/dl)	15.9 ± 0.5	12.1 ± 0.6	<0.0001
Preoperative serum level of AFP (ng/ml)	1,71,487 ± 32,439	2,81,387 ± 40,664	0.0394
Preoperative hemoglobin (g/dl)	14.7 ± 0.5	12.6 ± 0.6	0.0143
Preoperative platelet number (10^4/μl)	32.8 ± 2.1	21.8 ± 2.5	0.0012
Amount of bleeding at operation (ml)	74.7 ± 48.8	414.9 ± 59.4	<0.0001

Table 2 Univariate analysis of nominal scale data of tumor histology

Characteristics	Mature teratoma	Immature teratoma	*P* value
Maternal complication			0.015
Yes	9	14	
No	41	19	
Mode of delivery			0.0076
Emergency cesarean section	11	18	
Vaginal delivery	13	3	
Planned cesarean section	25	12	
Type of tumor component			0.0007
Cystic type	18	2	
Predominantly cystic mixed type	22	11	
Predominantly solid mixed type	10	15	
Solid type	1	5	
Rapture of tumor capsule at birth			0.0007
Yes	5	14	
No	42	18	
Bleeding from the tumor at birth			0.0006
Yes	1	9	
No	45	22	
Subcutaneous edema			0.0053
Yes	1	7	
No	44	25	
Need for mechanical ventilation			<0.0001
Yes	8	20	
No	39	11	
Catecholamines administration			<0.0001
Yes	5	16	
No	42	14	
Blood transfusion after delivery			<0.0001
Yes	1	13	
No	45	17	
Preoperative DIC			0.0129
Yes	1	5	
No	46	22	
Preoperative blood transfusion			0.0006
Yes	3	11	
No	44	18	
Laparotomy			0.0099
Yes	10	14	
No	37	14	
Surgical position			0.0044
Supine	5	10	
Decubitus	0	1	
Prone	35	10	
Multiple	7	8	
Intraoperative transfusion			<0.0001
Yes	16	26	
No	31	3	
Intraoperative resuscitation			0.0019
Yes	1	7	
No	46	21	
Postoperative DIC			0.0027
Yes	2	8	
No	45	20	
Intracranial hemorrage			0.0084
Yes	0	4	
No	46	24	
Postoperativemotor disturbance of the lower limbs			0.0019
Yes	1	6	
No	45	17	
Outcomes			0.0437
Termination	2	1	
IUFD	1	1	
Dead after birth	2	8	
Alive	46	23	

three cases and predominantly cystic mixed tumors, predominantly solid mixed tumors and solid tumors were each observed in one case. The maximum diameter of the primary tumor ranged from 5.5 to 18 cm. The histological diagnosis of the primary tumor included four mature teratomas and two immature teratomas.

The age at recurrence ranged from 7 to 16 months. Recurrence with a malignant component was detected in five cases, and all malignant components, except for that observed in case 3, were diagnosed as yolk sac tumors. Two of the five patients with malignant components initially developed recurrence with benign tumors; however, yolk sac tumors later appeared.

All six patients were successfully treated with either surgery alone or surgery with chemotherapy. Repeated surgery was required in three cases. The number of courses of chemotherapy ranged from three to five in the patients with malignant components. The follow-up periods ranged from 22 to 72 months. All six patients are currently alive without any tumors.

Discussion

Several reports regarding the histology of SCTs have so far been published. De Backer et al. [5] performed a retrospective institutional review of 70 patients and reported that mature teratomas were observed in 48 patients, immature teratomas were observed in 11 patients and yolk

Table 3 Clinical features of the patients with recurrence

Case no.	1	2	3	4	5	6
Gestational age at delivery (weeks)	38	40	33	41	35	33
Gender	F	M	M	F	M	M
Birth weight	3,140	3,252	3,443	3,274	3,130	4,615
AFP (ng/ml) at birth	18,051.5		2,33,252		3,71,520	1,77,900
Age at primary operation (day)	11	21	1	10	6	1
Altman's classification	III	III	II	III	I	I
Type of tumor component	Cystic	Cystic	Solid	Predominantly cystic mixed	Predominantly solid mixed	Cystic
Extent of resection	Total	Total	Subtotal	Total	Total	Total
Primary tumor weight (g)			1,000	226	768	2,100
Maximum diameter of the primary tumor (cm)	5.5	11	18	7	18	13.6
Histology of the primary tumor	Mature	Mature	Immature	Mature	Mature	Immature
Age at recurrence (months)	12	9	9	12	16	7
Site of recurrence	Local	Local	Local	Local and lung	Local	Local
Histology of recurrent tumor	Malignant	Mature → malignant	Unknown (malignant susp.)	Malignant	Benign → malignant	Mature
Number of operations after recurrence	1	2	2	1	2	1
Chemotherapy	4 courses	3 courses	3 courses	5 courses	3 courses	No
Follow up period (months)	29	22	72	37	26	24
Outcome	Alive without tumor	Alive without tumor	Alive without tumor	Alive without tumor	Alive without tumor	Alive without tumor

sac tumors were observed in nine patients. The UKCCSG study reported that 66 patients with nonmalignant SCTs were diagnosed with mature teratomas and 32 patients were diagnosed with immature teratomas [7]. On the other hand, histological information exclusive to prenatally diagnosed or neonatal SCT is scarce. The UKCCSG study reported results exclusive to newborns less than 4 weeks of age showing that 27 neonates had mature teratomas, 16 neonates had immature teratomas and six neonates had malignant teratomas at the initial diagnosis [8]. In our study, 61, 39 and 0 % of the patients were diagnosed with mature teratomas, immature teratomas and malignant teratomas, respectively. Although the distribution of mature and immature teratomas in this study is similar to that reported in previous studies, we did not find any yolk sac tumors in our patient series. In our study, all patients were diagnosed prenatally. It is possible that yolk sac tumors are rare in patients with prenatal SCT and are usually diagnosed postnatally. An alternative explanation is the possibility of differences in the pathological diagnosis. We assessed the pathological diagnoses determined by local pathologists at each institute. It is uncertain how precisely or carefully small malignant foci in large tumor specimens of prenatally diagnosed SCT were assessed at the individual hospitals.

Tapper et al. [4] reported that there are no significant differences in age or tumor type according to Altman's classification among children with mature versus immature teratomas, although immature teratomas are significantly larger than mature teratomas. That study included both patients with prenatal SCT and older patients with SCT. Sheth et al. [9] evaluated the prenatal sonograms of 15 fetuses with SCT and concluded that there is no correlation between the sonographic appearance and the presence of immature or malignant components. In the present study, we evaluated the sonographic appearance of tumors in 84 SCT patients and found a significant correlation between the prenatal sonographic appearance and the histological diagnosis. Larger tumors, rapidly growing tumors and solid component-dominant tumors tended to be diagnosed as immature teratomas.

Moreover, the patients with immature teratomas were in significantly poorer perinatal condition than the patients

with mature teratomas. A lower gestational age at delivery, Apgar scores, hemoglobin level and platelet count were strongly associated with a diagnosis of immature teratoma. Graf et al. [10] reported the findings of a clinical trial of preterm SCT debulking. They found tumor maturation in tumor specimens obtained during delivery or autopsy compared with that observed in the initially examined tumor specimens obtained at the time of debulking. The authors suggested that maturation of SCT may naturally occur during gestation. This speculation possibly applies to our results. In this study, the fetuses with rapidly growing large tumors tended to be delivered at an earlier gestational age with immature tumors. The clinical condition of immature neonates with large and fragile tumor is poor. It has been reported that the overall mortality rate of children with mature teratomas is significantly lower than that of children with immature tumors [4]. Our data suggest that the poorer outcomes observed in patients with immature teratomas are not due to the aggressiveness of the tumor cell biology, but rather possibly to the poorer condition of neonates with immature teratomas.

Recurrence of SCT has been reported in several studies. Tapper et al. [4] reported that, among their 54-year experience at the Children's Hospital Medical Center and Harvard Medical School, 2 of 73 mature teratomas recurred, while three of 20 immature teratomas recurred. In the UKCCSG study [7], 18 of 98 sacrococcygeal teratomas, including non-neonatal cases of mature and immature histological tumors, recurred. Of the 18 tumors which were observed at recurrence, six were mature teratomas, three were immature teratomas and nine were malignant teratomas. De Backer et al. reviewed previous studies reporting recurrence rates for SCT. Overall, recurrence was observed in 2–35 % of cases. For mature teratomas, the recurrence rate ranges from 0 to 26 %, while that for immature teratomas is higher, ranging from 12 to 55 %. The authors discussed several possible factors for recurrence, that is, failure to achieve complete resection of the tumor, en bloc removal of the coccyx along with the tumor, tumor spillage and failure to detect malignant components within the tumor [5]. Derikx et al. evaluated the factors associated with recurrence and metastatic disease in 173 children with SCT in the Netherlands. Nineteen children developed recurrence of SCT at a median interval of 10 months (range 32 days to 35 months) after undergoing primary surgery. The risk factors for recurrence included pathologically confirmed incomplete resection (odds ratio (OR) 6.54) and an immature (OR 5.74) or malignant histology (OR 12.83). The tumor size, Altman classification, patient age and decade of diagnosis were not found to be risk factors for recurrence. One-third of the recurrent tumors exhibited a shift towards histological immaturity or malignancy compared with the primary tumor. The authors concluded that SCT recurs in 11 % of children within 3 years of surgery. Mature teratomas have the biological capability to become malignant. In our series, 6 of 72 patients exhibited recurrence, five of whom had a malignant component in the recurrent tumor. The histology of the initial tumor included four mature teratomas and two immature teratomas. Complete resection was achieved in five of the six patients at the initial resection. Although the number of patients was small, our data suggest that neither an immature histology nor incomplete resection contribute to recurrence. In line with the findings of previous studies, all cases of recurrence were detected before 2 years of age. Five patients with malignant components underwent chemotherapy. All six patients are currently alive without tumors at 22–72 months of follow-up. Bilik et al. [11] recommended that close follow-up (including frequent examinations, measurement of the serum alpha-fetoprotein level and diagnostic imaging) be provided for at least 3 years for all patients having undergone excision of SCT in the newborn period.

In conclusion, in this study, mature teratomas were the most commonly observed histological type, accounting for 61 % of prenatally diagnosed SCTs. No malignant teratomas were observed, in contrast to the findings of previous studies. The patients with immature teratomas were more likely to have a poor neonatal condition and an increased risk of mortality, suggesting that the poorer outcomes observed in patients with immature teratomas are not due to the aggressiveness of the tumor cell biology, but rather possibly to the poorer conditions of neonates with immature teratomas. Late recurrence was observed in 8.3 % of cases. In our observations, neither an immature histology nor incomplete resection appeared to contribute to recurrence. Five of six patients with recurrence had a malignant component, and all cases of recurrence were detected before 2 years of age. Therefore, providing close follow-up (frequent examinations, measurement of the serum alpha-fetoprotein level and diagnostic imaging) for at least 2–3 years is recommended for all patients having undergone excision of SCT in the newborn period.

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References

1. Isaacs H Jr (2004) Perinatal (fetal and neonatal) germ cell tumors. J Pediatr Surg 39:1003–1013
2. Usui N, Kitano Y, Sago H, Kanamori Y, Yoneda A, Nakamura T, Nosaka S, Saito M, Taguchi T (2012) Outcomes of prenatally diagnosed sacrococcygeal teratomas: the results of a Japanese nationwide survey. J Pediatr Surg 47:441–447
3. Olson TA, Schneider DT, Perlman EJ (2011) Germ Cell Tumors. In: Poplack DG (ed) Pizzo PA. Lippincott-Raven Publishers, Philadelphia, Principles and Practice of Pediatric Oncology, pp 1045–1067
4. Tapper D, Lack EE (1983) Teratomas in infancy and childhood: a 54-year experience at the Children's Hospital Medical Center. Ann Surg 198:398–410
5. De Backer A, Madern GC, Hakvoort-Cammel FG, Haentjens P, Oosterhuis JW, Hazebroek FW (2006) Study of the factors associated with recurrence in children with sacrococcygeal teratoma. J Pediatr Surg 41:173–181 (discussion 173–181)
6. Altman RP, Randolph JG, Lilly JR (1974) Sacrococcygeal teratoma: American Academy of Pediatrics Surgical Section Survey—1973. J Pediatr Surg 9:389–398
7. Mann JR, Gray ES, Thornton C, Raafat F, Robinson K, Collins GS, Gornall P, Huddart SN, Hale JP, Oakhill A (2008) Mature and immature extracranial teratomas in children: the UK Children's Cancer Study Group Experience. J Clin Oncol 26:3590–3597
8. Huddart SN, Mann JR, Robinson K, Raafat F, Imeson J, Gornall P, Sokal M, Gray E, McKeever P, Oakhill A, Children's Cancer Study G (2003) Sacrococcygeal teratomas: the UK Children's Cancer Study Group's experience, I. Neonatal. Pediatr Surg Int 19:47–51
9. Sheth S, Nussbaum AR, Sanders RC, Hamper UM, Davidson AJ (1988) Prenatal diagnosis of sacrococcygeal teratoma: sonographic-pathologic correlation. Radiology 169:131–136
10. Graf JL, Housely HT, Albanese CT, Adzick NS, Harrison MR (1998) A surprising histological evolution of preterm sacrococcygeal teratoma. J Pediatr Surg 33:177–179
11. Bilik R, Shandling B, Pope M, Thorner P, Weitzman S, Ein SH (1993) Malignant benign neonatal sacrococcygeal teratoma. J Pediatr Surg 28:1158–1160

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