The THAI Journal of SURGERY

Official Publication of the Royal College of Surgeons of Thailand

Vol. 21 July - September 2000 No. 3

Germ Cell Tumors in Children

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Abstract **A retrospective review of 119 cases of germ cell tumors (GCT) in children who were treated at the Queen Sirikit National Institute of Child Health during 1987-1996 revealed teratomas in 87 percent, pure endodermal sinus tumor (EST) 10 percent and other GCT 3 percent of all patients. Of the 103 cases of teratomas, 80 were mature, 14 immature and 9 malignant teratomas.**

Tumors were located in the sacrococcygeal area in 37 cases, ovary 30 cases, retroperitoneal area 21 cases, testis 12 cases, mediastinum 11 cases, central nervous system 6 cases, and others 2 cases.

Female to male ratio was about 2:1. Female predominance was noted in tumors of lower part of the body where as male predominance was upper part of the body. The numbers of male and female patients were almost equal in retroperitoneal GCT.

Behavior of GCT did not depend entirely on the histology of the tumors only, but also on the location of the tumors and the age at time of diagnosis and treatment. Immature teratomas behaved as benign tumors in most locations, except in the ovary of prepubertal or pubertal girls, where they behaved as malignant tumors.

Serum alpha fetoprotein (AFP) level correlated with the presence of EST component in tumors. Postoperative monitoring of serum AFP level appeared to be important in the long-term follow-up. Patients with GCT should be closely followed up for at least 3 years postoperatively.

Germ cell tumors (GCT) originate from primordial germ cells. Five main histologic categories include germinoma (dysgerminoma in the ovary, seminoma in the testis), embryonal carcinoma, endodermal sinus tumor (EST, yolk sac tumor, infantile embryonal carcinoma) and teratoma.[1] A mixture of more than one histologic types in one tumor is not uncommon. The first 4 histologic types are unequivocally malignant, while a teratoma may behave as either a benign or malignant tumor.

Much confusion and controversy exist regarding classification and behaviour of teratomas. Some authors classify teratomas into 2 histologic types : mature and immature teratomas.[1-3] Histologic grading system from grade 0 to grade 3 is based on the amount of immature component in the tumor.[2,3] Some reports prefer to classify teratomas into 3 histologic types : mature, immature and malignant teratomas.[4-6] Others simply divide teratomas into "benign" and "malignant" teratomas.[7-8] In some reports, other GCT are also included under the name "teratoma".[5,7-10] For unclear reason, the behavior of teratomas does not depend entirely on their histologic appearance only, but also on the age at diagnosis and location of the tumors.[1,5,10-13]

This communication reports the experience with these tumors at the Queen Sirikit National Institute of Child Health, Bangkok, during the years 1987-1996.

Materials and Methods

A retrospective review of medical records of the patients who were treated in the Department of Surgery at the Queen Sirikit National Institute of Child Health, formerly Children's Hospital, for germ cell tumors during the 10-year period between 1987 and 1996 was carried out. A total of 119 cases were available for the study. The data were collected from existing medical records for epidemiologic study as well as diagnostic and therapeutic problems. Pathologic diagnoses were based on pathological reports in the patients' records. Almost all of these were reports from the Institute of Pathology, Department of Medical Services, Ministry of Public Health. No attempt was made to review the histologic slides.

A tumor was labelled as a "mature teratoma" if it was composed of only mature teratomatous components and as an "immature teratoma" if it contained immature tissue and without other malignant component. A tumor was labelled as a "malignant teratoma" if it contained both teratomatous tissues and any of the other 4 malignant GCT. If a pathologic report indicated that more than one type of malignant GCT were present in the tumor without mentioning the presence of teratomatous component, the tumor was designated as a "malignant mixed GCT" in this study.

Sacrococcygeal GCT was classified into 4 anatomical types as described by Altman et al.[11]

Preoperative alpha-fetoprotein (AFP) determination was available for the study in only 60 cases. Normal ranges of AFP levels for different age groups during infancy were determined on the basis of the graphs by Tsuchida et al[14] and Ohama et al.[15] The AFP level of 20 ng/ml or lower is considered as normal for older children.[16,17]

Results

1. *Histologic types and locations of tumors*

The frequency of each histologic type and site of origin of tumors are shown in Table 1. The most common GCT was teratoma, accounting for 87 percent

Table 1 Histologic types and locations.

Location	Teratoma			Endodermal sinus tumour	Germinoma	Mal. Mixed GCT	Total
	Mature	Immature	Malignant				
1. Sacrococcygeal area	27	3	3	4	-	-	37
2. Ovary	20	5	2	2	1	-	30
3. Retroperitoneal area	16	4	-	-	-	1	21
4. Testis	4	1	2	5	-	-	12
5. Mediastinum	7	1	2	-	1	-	11
6. Central nervous system	5	-	-	-	1	-	6
7. Neck	1	-	-	-	-	-	1
8. Vagina	-	-	-	1	-	-	1
Total	**80**	**14**	**9**	**12**	**3**	**1**	**119**

of all cases. Of the 103 cases of teratomas, 80 were mature, 14 immature and 9 malignant teratomas. The malignant component in the latter was EST in all cases.

The most common site of the tumors was the sacrococcygeal (SC) region, accounting for 32 per cent of all cases, while the ovary ranked the second, accounting for 26 percent.

2. *Sex incidence*

Of the total 119 cases, 38 were male and 81 were female. The overall male to female ratio was 1:2.1 (Table 2). It was noticeable that female predilection was most obvious in tumors of lower part of the body but male predilection was most obvious in tumors of upper part of the body. Sex incidences were almost equal in the retroperitoneal GCT.

3. *Age at surgery*

Age at surgery is shown in Figure 1. About half of the total number of patients were operated upon within one year of age. Of the total 60 infants who had surgery within one year of age, 30 had surgery done within 3 months of age. Twenty-two of the latter had sacrococcygeal teratoma (SCT).

4. *Clinical manifestation, treatment and results*

4.1 Sacrococcygeal tumors

Of the 37 cases of SC tumors, 34 were SCT and 3 were pure EST. Twenty-seven patients had mature teratoma, 3 had immature teratoma and the

Table 2 Male to female ratio.

Location of Tumors	M : F Ratio
1. Sacrococcygeal area	1 : 3.6
2. Gonad	1 : 2.6
3. Retroperitoneal area	1 : 1.3
4. Mediastinum	2.7 : 1
5. CNS	6 : 0
Overall	1 : 2.1

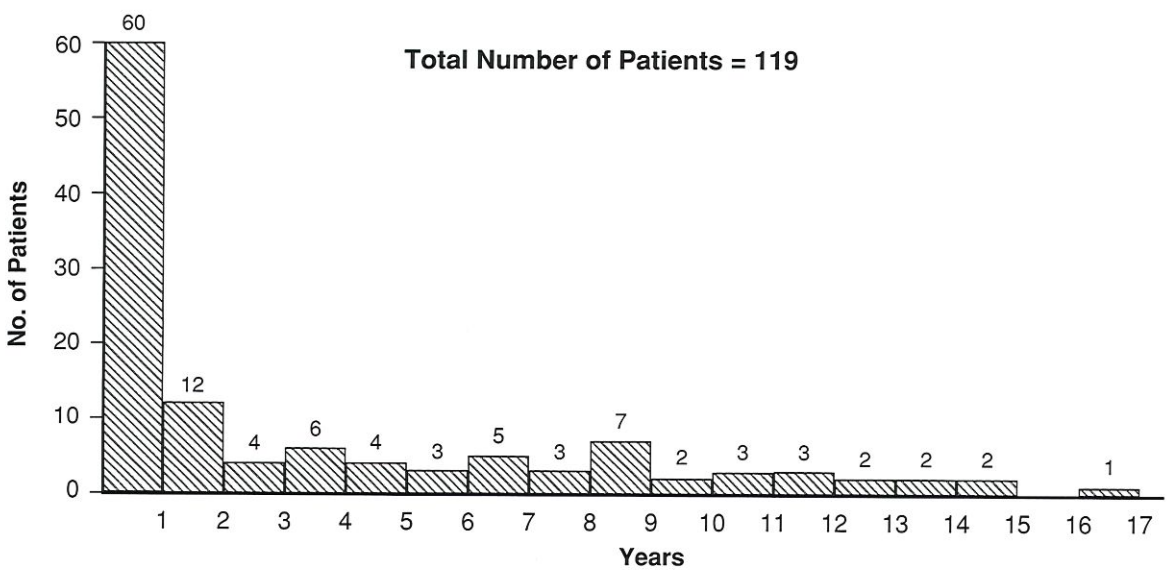

Fig. 1 Age at surgery.

remaining 4 patients had malignant teratoma. The overall incidence of malignancy in SC tumors was about 19 percent.

All the 3 cases of immature teratoma were treated with excision in the newborn period without chemotherapy or irradiation. Their behavior appeared benign. However, one of these 3 cases had surgery done elsewhere before referral. The tumor was probably of type II. The presacral portion of the tumor had previously been incompletely removed. The patient subsequently had two repeated excisions at our hospital. In both occasions, the residual tumor showed only mature teratomatous components.

Of the 27 cases of mature teratoma, one with type IV tumor had an incomplete resection of the tumor done elsewhere through an abdominal approach at the age of 2 months before referral. She needed a repeated resection of the tumor at our hospital through a combined abdomino-sacral approach and coccygectomy.

Risk of malignancy in various types of SC tumors is shown in Table 3. The risk was zero in type I and 50 percent in type IV.

When ages at surgery were taken into consideration, it was found that none of the 29 patients who had tumor excision at the age less than 12 months had malignant tumor, while 87.5 percent (7 out of 8 patients) of those who had tumor excision after 12 months of age had malignant tumor.

Risk of malignancy in female patients appeared to be higher than that in the male : 24 percent (7 out of 29 female patients) versus 0 percent (none of 8 male patients).

The most common chief complaint in children with SC tumor was a SC mass since birth. This was noted in 29 of the total 37 cases. Other symptoms included constipation and /or dysuria in 6 cases and a palpable abdominal mass in 2 cases. All of these 8 cases had type IV tumor.

The large size of the SC tumors posed a great deal of problems for surgeons even in the cases of benign tumors. Three patients had rectal injury during surgery and one additional patient eventually developed a urethrovaginal fistula after multiple excisional procedures. When the tumor was malignant, much more difficulty was encountered during the excision attempts. Presumably complete excision of malignant SC tumors was accomplished in only one case, partial excision was performed in 2 cases and only a biopsy was performed in the remaining 4 cases.

Chemotherapy and irradiation were given to all of the cases of malignant SC tumors. The result of the treatment was disappointing. Three patients succumbed while on chemotherapy within one year after surgery. One patient, who had EST with lung metastasis on first admission, had partial excision of the primary tumor plus chemotherapy and irradiation, but never came back for a follow-up after her discharge from the hospital 4 months following surgery. She lived in Nakonsrithamaraj Province, in southern part of Thailand. One patient had biopsy only for a malignant teratoma, plus chemotherapy and irradiation. The presacral mass disappeared completely but she was lost to follow-up 2 months after surgery. The 2 remaining patients with distant metastasis were lost to follow-up 6 months and 29 months after surgery respectively.

All of the patients with mature and immature teratomas had tumor excision only. None had come back with metastasis.

4.2 Ovarian tumors

Of the total 30 cases of ovarian tumors, 27

Table 3 Risk of malignancy in sacrococcygeal GCT.

Type	Total Number	Patients with Malignancy	Per cent
I	16	0	0
II	8	1	12.5
III	3	1	33.3
IV	10	5	50.0
Total	**37**	**7**	**19**

Table 4 Age distribution of ovarian GCT.

Age (Yr.)	Teratoma			EST	Dysgerminoma	Total
	Mature	Immature	Malignant			
<1	-	-	-	-	-	0
1-5	8	1	0	0	0	9
5-10	7	3	1	1	1	13
>10	5	1	1	1	0	8
Total	**20**	**5**	**2**	**2**	**1**	**30**

were teratomas, 2 pure EST and one was dysgerminoma (Table 1).

All of the patients with malignant GCT were over 5 years of age at the time of diagnosis (Table 4). One patient with immature teratoma was 4 years old but the tumor was a grade 1 teratoma, which was considered to be a benign tumor.[2,17-20]

Chief complaints included palpable abdominal mass in 16 cases, and abdominal pain in 18 cases. One had chronic fever and weight loss. Seven patients with acute abdominal pain were found to have twisting of their ovarian tumors.

Of the 5 cases of immature ovarian teratoma, 2 were found to have gliomatosis peritonei. One of these 2 patients had grade 2 immature teratoma in the left ovary, but the peritoneal implants were found to be of grade 1 teratoma. She was treated with a unilateral salpingo-oophorectomy (USO) and postoperative chemotherapy. She was still alive without evidence of tumor at the time of this review, 9 years after surgery. The other patient, who had a grade 3 teratoma in her right ovary, but the peritoneal implants were found to be mature glial tissue, underwent a USO plus chemotherapy and irradiation. The peritoneal implants became gradually larger postoperatively despite the treatment. Her general condition became worse and she was lost to follow-up about 2 years after surgery, presumably dead from her tumor. The third patient had a grade 1 teratoma and had a USO alone. She never came back for follow-up. The fourth patient had a grade 3 teratoma and underwent USO alone. She left the hospital refusing further adjuvant treatment and never came back. The fifth patient, who had a grade 2 teratoma, refused further adjuvant chemotherapy after USO. She was still alive and well at the time of this review, two and a half years after surgery.

Two patients with pure EST were treated by USO plus chemotherapy and irradiation. One of these 2 patients succumbed 5 months after surgery. The other had previously undergone a USO elsewhere for twisted ovarian tumor. According to the pathologic report, the histology of the ovarian tumor was of uncertain nature because of the hemorrhagic necrosis of the tumor. When she was referred to our hospital 8 months later, she was found to have a large abdominal mass. Exploratory laparotomy at our hospital revealed a large tumor mass in the omentum. This mass was excised and the histologic examination showed an EST. She subsequently received chemotherapy and irradiation. However, after only one course of chemotherapy, she was transferred to another hospital for further treatment on the parents' request. The final result of the treatment was, therefore, not known.

The patient with dysgerminoma in her right ovary had a USO in the first operation. One month later, she had thoracotomy for a mediastinal mass and a biopsy showed caseating granuloma. She never came back for further treatment and, therefore, the long term result was not known.

4.3 Testicular tumors

Of the 12 testicular GCT, 7 were malignant and 5 were benign (Table 1).

All but one of the patients came to hospital with a painless testicular enlargement. The only exception was a 4-month-old boy who came with the chief complaint of abdominal distension. He was found to have an 8-cm mass in the left lower quadrant of the abdomen. The left testis was not palpable in the scrotum. The abdominal mass was removed and the histologic examination reported a mature teratoma

arising in an undescended testis.

Age at diagnosis ranged from 4 to 45 months with the mean age of 16 months for benign tumors, and from 3 to 29 months with the mean age of 14 months for malignant tumors. There was no statistical significance between the two groups.

Of the 4 patients with mature teratoma, 3 had a radical inguinal orchidectomy (transinguinal removal of the testis and the spermatic cord) and the remaining one, who had teratoma of the intraabdominal testis, had a transabdominal removal of the tumor. The patient with a grade 3 immature teratoma also had radical orchidectomy alone without further treatment. None of these 5 cases had a recurrence or metastasis.

Of the 2 cases of malignant teratoma, one had previously had a trans-scrotal orchidectomy done elsewhere and the histologic examination showed a combination of immature teratoma with EST. He subsequently underwent hemiscrotectomy, excision of the spermatic cord and unilateral para-aortic node dissection[21] at our hospital. No residual tumor was noted. He received 2 courses of chemotherapy and was subsequently lost to follow-up 3 months after surgery. The other patient underwent a radical inguinal orchidectomy at the age of 3 months at our hospital. Histologic examination showed a combination of grade 3 immature teratoma and EST. He subsequently received chemotherapy. He was alive and well without evidence of tumor at the time of this review, 3 years postoperatively.

Of the 5 cases of pure EST, one had an inguinal orchidectomy done elsewhere at the age of 2 years. A histologic examination showed EST with focal vascular invasion in the spermatic cord. When he was referred to our hospital one month later, he was found to have a large abdominal mass and also a mass in the left supraclavicular area. A sonographic study of the abdomen showed a large abdominal mass and multiple intrahepatic lesions, presumably metastases. Biopsy of the supraclavicular mass revealed metastatic EST. The parents refused further treatment. Of the remaining 4 cases, only one patient had a radical inguinal orchidectomy done as an initial procedure in our hospital, but the other 3 patients had a simple orchidectomy done elsewhere before referral to our hospital. The testis was removed through a scrotal incision in 2 latter cases and through an inguinal incision in the other one. At our hospital, a hemiscrotectomy and a transinguinal removal of the spermatic cord were done in the first 2 cases, and the mentioned procedure plus excision of previous surgical scar in the groin in the last case. Of the last 4 cases, 2 also had a unilateral para-aortic node dissection as well. The specimen tissue showed no metastasis in these 2 cases. All 4 cases had postoperative chemotherapy without irradiation. Three of these 4 cases were alive and well without evidence of metastasis at 4 years, 6 years and 9 years and 8 months postoperatively. The long-term result of the fourth case was not known because of incomplete information of his follow-up record.

4.4 Retroperitoneal germ cell tumors

Of the 21 cases of retroperitoneal germ cell tumors (RGCT), 20 were teratomas and one was a malignant mixed GCT (Table 1). Sixteen cases of teratomas contained only mature components, and 4 had immature teratomatous tissue as well. Of the 4 cases of immature teratoma, only one, who was operated upon at the age of 3 months, was reported to have grade 3 teratoma which was considered a malignant tumor. She received postoperative chemotherapy and was alive without evidence of recurrence or metastasis at the time of this review, 8 years postoperatively. The remaining 3 patients were considered to have benign tumors and none of these came back with tumor recurrence or metastasis.

All but one of the patients came to hospital with the chief complaint of either abdominal enlargement or palpable abdominal mass. The only exception was a 3-month-old boy who went to see a physician for abdominal pain. He was then found to have a palpable abdominal mass. One newborn infant, who was born by cesarean section because of prolonged second stage of labor, had a large abdominal mass that caused respiratory difficulty since birth.

Nine patients were male and 12 patients were female. The male to female ratio was 1:1.3.

Age at surgery ranged from newborn period to 8 years and 9 months. The oldest patient was an 8-year-and-9-month-old girl who had malignant mixed GCT. All but 2 of the patients with teratoma were operated upon at the age below 12 months. The remaining 2 cases were 3 years and 5 years and 5 months of age. Both of the latter had mature teratoma.

All but one of the patients with teratoma were treated by tumor resection only. The remaining

one, who had a grade 3 immature teratoma, had postoperative chemotherapy after tumor resection.

One newborn girl, who was born by cesarean section as previously mentioned, underwent an emergency laparotomy and tumor resection at the age of one day due to respiratory failure from huge teratoma. She required ventilatory support post-operatively and eventually expired 17 days after surgery because of respiratory failure. This was the only patient who expired due to postoperative complication. The rest of the cases with teratoma did well postoperatively. No recurrence or metastasis was noted.

The patient with malignant mixed GCT had tumor biopsy only because the tumor was not resectable. She received chemotherapy and irradiation but the tumor did not respond to treatment. She was lost to follow-up 6 months postoperatively, presumably dead at home.

4.5 Mediastinal germ cell tumors

Of the 11 cases of mediastinal GCT, 7 were mature teratoma, one grade 2 immature teratoma, 2 malignant teratoma and one germinoma (Table 1).

Seven were male and 4 were female. Four patients were operated upon at the age below one year, one at the age of one year and 11 months, and the remaining 6 patients at the age between 6 to 11 years. All 3 cases of malignant tumor were operated upon at the age above 7 years.

Most patients had fever, cough and breathing difficulty. One patient also had chest pain. Chest film showed calcifications in 5 of the 7 cases of mature teratoma, and in all cases of immature and malignant teratomas, but not in the case of germinoma.

Complete excision was accomplished in all cases of mature and immature teratomas, but in only one of the two cases of malignant teratoma. Only partial excision was done in the other case of malignant teratoma and the case of germinoma. The patient who had complete excision of malignant teratoma also had postoperative irradiation and chemotherapy. He did well without recurrence or metastasis during the period of 4 years following surgery, after which he was lost to follow-up. The other patient who had partial excision of malignant teratoma refused further treatment. He succumbed at home one month postoperatively. The patient with germinoma received postoperative irradiation and chemotherapy. His parents refused further treatment after 2 months postoperatively and never came back for a follow-up.

None of the patients with mature and immature teratomas came back with recurrence or metastasis.

4.6 CNS germ cell tumors

Only 6 cases were histologically proved to have CNS GCT. Four were intracranial mature teratoma, one was mature teratoma of the spinal cord, and one was intracranial germinoma. Of the 4 cases of intracranial mature teratoma, one was 10 months old and the other 3 were 6, 12 and 13 years old respectively. The patient with germinoma was 14 years old and the patient with spinal cord teratoma was one year and one month old.

4.7 Cervical germ cell tumor

The only case of cervical GCT was a 4-year-old girl whose chief complaint was a swelling under the chin since birth. Roentgenogram of the mass showed no calcification. Excision of the mass showed a mature teratoma and there was no recurrence or metastasis.

4.8 Vaginal germ cell tumor

The patient, who was 6 months old at presentation, came with vaginal bleeding. A mass was palpable in the suprapubic area as well as in the vagina. Serum AFP level was over 20,480 ng/ml. Biopsy of the vaginal mass showed EST. Exploratory laparotomy revealed a large mass in the pelvic cavity. It was considered non-resectable. Biopsy of the pelvic mass also showed EST. She received irradiation and chemotherapy of VAC protocol. The mass became gradually smaller and eventually completely disappeared. Serum AFP level also gradually decreased and was eventually not detectable. She was well, without evidence of tumor, at the time of this review 9 years after the initial biopsy.

5. Serum AFP level

Of the total 60 patients, in whom the preoperative AFP level was available for the study, 38 had mature teratoma. All of these 38 patients had AFP level within normal limits for their age.[14-17] Of the 10 cases of immature teratomas, 4 had AFP level within normal ranges for their ages, and 6 had AFP level above the normal ranges (4 ovarian immature teratomas, 2 retroperitoneal immature teratomas). The remaining 12 cases who had either pure EST or malignant teratoma containing EST had elevated level of AFP.

Discussion

About 87 percent of all GCT in our series were teratomas. This was rather high when compared to 62 per cent in population-based survey from Manchester, UK by Marsden et al.[22] Sacrococcygeal region appeared to be the most common location of GCT in our series, similar to those data of teratoma from USA.[4,8,10,23] In contrast, reports from UK and Germany indicated that ovarian teratomas were more common than SCT.[22,24] The difference may be due to the fact that our data, as well as those from USA, were from hospital-based studies, while those of Marsden et al[22] were from a population-based survey. It was possible that difficult cases like sacroccygeal tumors were most often referred to tertiary care centers while some of ovarian tumors were handled in general hospitals.

Retroperitoneal area was a rare location of GCT in Western countries, representing only about 5 per cent of GCT.[1,4,8,16,22-24] However, in our present series, it appeared to be a much more common location of GCT, representing about 18 percent of all GCT. Experience from Ramathibodi Hospital,[25] as well as our previous report,[26] indicated that the occurrence of retroperitoneal teratoma in Thailand appeared to be more common than those reported in the literature.

Mature teratomas in children usually behave as benign tumors if a complete excision is accomplished. Recurrence occasionally occurs, especially after a resection of large SCT. The recurrent tumor is usually composed of mature teratomatous tissue. However, instances of malignant recurrence after previous excision of histologically mature SCT have been reported.[5,8,10,23,24,27] This may be due to the presence of malignant component in the primary tumor but not being recognized during histologic examination as a result of sampling error in large tumor. Incomplete removal of such malignant component may result in tumor recurrence.

The presence of any malignant component of GCT, i.e. EST, embryonal carcinoma, germinoma or choriocarcinoma, in a teratoma is obviously indicative of malignancy. However, the mere presence of immature or embryonic somatic tissue in a teratoma without apparent malignant germ cell component poses a difficult prognostic problem. Immature teratomas behave differently in different locations and different age groups. The presence of immature component does have adverse effect on the prognosis of ovarian teratoma in prepubertal or pubertal girls,[1,2,23,28,29] but does not have such effect when it is present in infantile SCT, testicular teratoma or extragonadal teratoma during childhood.[1,2,12,13,30,31] Ovarian immature teratoma, without other malignant component, has been regarded as a malignant tumor and adjuvant chemotherapy has been recommended after salpingo-oophorectomy for grade 2 or 3 immature teratoma.[18-20]

On the other hand, testicular teratomas in adult, either mature or immature, behave as malignancy as they have been reported to have incidence of metastasis of 20-30 percent.[1,31]

The risk of malignancy in SCT is related to its anatomical type and age at surgery. Type I tumor has the lowest risk of malignancy and type IV has the highest risk. This was well demonstrated in our series, similar to the report by Altman et al.[11] In the American Academy of Pediatrics survey, the incidence of malignancy was 7 - 10 per cent if the tumors were operated upon at the age less than 2 months, but 48 - 67 per cent if treated after 2 months of age.[11] In our present series, the incidence of malignancy was 87.5 per cent if the tumors were treated after 12 months of age. These findings indicated that a SCT should be treated surgically as soon as possible after birth.

The large size of the SCT is a major problem for a complete excision. In many of our patients, tumors had been removed incompletely elsewhere before referral to our hospital. In some of type III tumors, a complete resection required a combined abdomino-sacral approach. The coccyx is to be removed along with the tumor in every case. Failure to remove the coccyx results in high recurrence rate.[8,9,24]

AFP is mainly produced by the liver, yolk sac and gastro-intestinal tract during fetal life. Serum AFP level reaches its maximum at about 13 weeks of gestation, and decreases gradually thereafter.[15] After birth, serum AFP level continues to decrease gradually. The decline rate of serum AFP level is not rectilinear. It is rapid during early newborn period but gradually slower until 8 months of age, when it reaches adult level.[14,15,17] Normal ranges of serum AFP level at different ages in normal individuals have been studied by Tsuchida et al[14] and Ohama et al.[15] Normal ranges for ages established by these studies have to be used to interpret

the value of individual AFP level. The data in this study, as well as others,[8,10,16,17] indicate that the presence of yolk sac tumor or EST is usually associated with elevated serum AFP level. In some patients with immature teratoma, without EST component, the serum AFP levels are also elevated.[10,16] The reason for this elevated AFP level is not clear. Could this be due to the unrecognized presence of minute foci of EST in such tumors?

The determination of serum AFP level is not only useful for the diagnosis of EST, but it is also helpful to determine the completeness of tumor removal and tumor recurrence during follow-up period.[10,14-17,22] Monitoring of serum AFP levels should be carried out at regular intervals for at least 3 years, because cases of malignant recurrence that were clinically recognized later than 2 years after excision of mature teratoma have been reported.[10,24]

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