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Original Article

Germ Cell Neoplasms of Sacrococcygeal Region: Clinical Characteristics, Outcomes and Analysis of Recurrence after Treatment; A Comprehensive 20-Year Single Center Study

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ABSTRACT

Aim: This study aimed to evaluate the clinical characteristics and outcomes of recurrent sacrococcygeal germ cell tumors (SC-GCTs).

Materials and Methods: This study was conducted with patients diagnosed with SC-GCTs between 2002 and 2022. Epidemiology, diagnostic and treatment methods, anatomic/histopathological classifications and recurrence were evaluated.

Results: This study included 55 patients (Female/Male: 45/10). According to Altman's-classification, 16 patients (29.1%) were Type I, 14 (25.5%) Type II, 12 (21.8%) Type III and 13 (23.6%) Type IV. Histologically, 69.1% of the lesions were mature teratomas, 14.5% were immature teratomas, and 16.4% were malignant teratomas. Eleven patients developed recurrent sacrococcygeal teratoma (recurrence age: 5 months-12 years). According to Altman's classification, 2/11 patients were Type II, 5/11 patients were Type III, and 4/11 patients were Type IV. The pathological results of the original tumors were mature teratoma in 4/11 patients, immature teratoma in 4/11 patients, and malignant teratoma in 3/11 patients. Malignant relapse with yolk sac tumor was detected in 6/11 patients, mature teratoma in 4/11 patients, and immature teratoma in 1/11 patients.

Conclusion: The risk of malignancy increases with age and Altman's Type III and IV. Recurrent tumors may have different histopathological types from the original tumor. The risk of recurrence as a malignant tumor after immature teratomas was higher than mature teratomas.

Keywords: Sacrococcygeal teratoma, recurrence, malignant teratoma

Introduction

Teratomas arise from germ cells or other totipotent cells (1-3). Primordial germ cells (PGCs) appear during the third week of gestation in the yolk sac wall near the allantois. They move along the dorsal mesentery of the hindgut, reaching the genital ridges by about the sixth week of gestation. A disturbed migration of PGCs results in misplacement at different sites in the body's midline. Extragonadal germ cell tumors (EGCT) are believed to develop after the malignant transformation of the residual PGCs (4). In another embryologic theory, sacrococcygeal teratomas (SCTs) develop at the base of the coccyx and are thought to be derived from Hensen's node (primitive knot) (5).

The incidence of SCT is approximately 1:27,000 (5) to 1:40,000 (6,7) live births. SCT is a rare tumor; however, it is still the most common fetal neoplasm and most common germ cell tumor (GCT) in infancy and early childhood (8).

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The patients can be classified anatomically by Altman's classification into 4 types (Type I: fully external, Type II: mainly external, Type III: mainly internal, Type IV: fully internal) (9), and histologically as mature, immature or malignant teratomas (1).

For decades, the diagnosis and treatment of SCTs have progressed and become standardized, and good prognosis is usually achieved. Nevertheless, increasing recurrent cases with poor survival rates have become a major challenge. Incomplete resection, tumor spillage, and residual coccyx have been identified as the main risk factors for recurrence. Previously published series have reported 2% to 35% recurrence rates (10,11).

This article aims to clarify any special characteristics in the history, clinical presentation, and outcomes of recurrent SC-GCTs.

Materials and Methods

This study was carried out in a pediatric surgery department in concordance with international ethical standards and the World Health Organization's Helsinki Declaration. This study was approved by the Ege University Faculty of Medicine, Medical Research Ethics Committee (approval no.: 20-11T/4) and informed consent was obtained for all subjects.

This study was performed retrospectively and included all SC-GCTs in a single center. The pertinent clinical information and available pathologic data were collected from 55 patients with germ cell neoplasms of the sacrococcygeal area from 2002 to 2022.

The demographics, time of diagnosis, clinical complaints and associated malformations were reviewed. Preoperative alpha-fetoprotein (AFP) levels were evaluated according to reference values according to the patients' ages (12). Radiological images were examined, and the patients were assigned into 4 groups according to Altman's classification (9). Surgical techniques, pathological results, and postoperative follow-up period were also investigated.

Those patients with recurrent diseases were evaluated. Time to recurrence, the predictive value of the level of AFP, and the role of magnetic resonance imaging (MRI) in diagnosing recurrent SC-GCTs and long-term outcomes were included in this study. Possible risk factors for recurrence were also evaluated. Statistical analyses were performed using the SPSS Statistics 26.0 version, including Pearson's chi-square test, ANOVA test, and the post-hoc test. A p value of <0.05 was considered statistically significant.

Results

This study included 55 patients with SC-GCTs treated at our center. There were 10 males and 45 females with a male-to-female ratio of 1 to 4.5.

Routine maternal ultrasonic examination identified the lesions prenatally in 19/55 patients. Fourteen patients were diagnosed at birth, and 10 patients were diagnosed in the infantile period. Twelve of 55 patients presented beyond the neonatal or infantile period. Most of the patients presented with sacrococcygeal mass (61%). The presentation symptoms and associated anomalies are given in Table I according to the patients' ages.

Detailed radiological examinations were made by ultrasonography (USG) (31/55 patients), MRI (44/55 patients), and computed tomography (CT) (4/55 patients). AFP levels ranged from 1- 455.075 ng/mL (mean: 58.560). Seven patients had higher AFP levels relative to nomograms according to their age.

Table I. Demographics and clinical status of the patients

Age at diagnosis	No of patients	Sex (M/F)	Clinical complaint	Associated anomalies
Prenatal	19 (34.5%)	3/16	Incidental sacrococcygeal mass in routine maternal USG No hydrops fetalis was detected	Meningocele 5.2% (1/19) ASD 5.2% (1/19)
0-28 days	14 (23.7%)	2/12	Sacrococcygeal mass	Currarino triad 7.1% (1/14)
29 days-1 year	3 (7.3%)	2/1	Swelling in the Sacrococcygeal area 66.6% (2/3) Constipation 33.3% (1/3)	Currarino triad 33.3% (1/3)
>1 year	19 (34.5%)	3/16	Constipation 42% (8/19) Swelling in the Sacrococcygeal area 15.7% (3/19) Weakness in the lower extremities 10.5% (2/19) Bruising in the genital area 10.5% (2/19) Difficulty in urination 15.7% (3/19) Frequent urination 5.2% (1/19)	Rectal duplication cyst (1/19) Currarino triad 5.2% (1/19) Anal stenosis 10.5% (2/19)

M/F: Male/Female, USG: Ultrasonography, ASD: Atrial septal defect

Sixteen (29.1%) patients were Altman Type I, 14 (25.5%) were Type II, 12 (21.8%) were Type III, and 13 (23.6%) were Type IV. Surgical resection was performed on all patients. The posterior sacrococcygeal approach was performed in 45 patients; 3 patients required an abdominal approach, and 7 patients required both. The surgical margins were free of tumor in the first operation in all patients.

Pathological examinations were reported as mature teratomas in 38 (69.1%), immature teratomas in 8 (14.5%), and malignant teratomas in 9 (16.4%) patients. Yolk sac tumor (YST) was detected in all malignant teratomas. The histopathological results are depicted in Table II and they are also grouped based on their preoperative Altman classifications.

One patient was referred to our clinic after having primary surgery elsewhere (a neurosurgeon had operated on this patient with a pre-diagnosis of meningomyelocele). However, the tissue biopsy performed intraoperatively revealed a yolk sac teratoma, and the patient was referred to our institution.

The patients were evaluated using the ANOVA test based on their Altman classifications and pathology results. A statistically significant relationship was found between the Altman classification and the pathology outcome (p=0.001). The risk of malignancy in Types III and IV according to the Altman classification was higher compared to Type I and II. It was 33.3% in Type III and 38.4 % in Type IV.

A post-hoc test was conducted to determine between which groups significant statistical differences existed. In this test, every Altman's type was compared with the other Altman's types. While no significant deference was found between Types I and II, and similarly between Types III and IV, significant differences were found when comparing Type I with Types III and IV, and also Type II with Types III and IV (Table III).

Adjuvant chemotherapy was given postoperatively in high-grade immature teratomas and malignant teratomas. Combinations of cisplatin, etoposide, and bleomycin (BEP) or carboplatin, etoposide, and bleomycin (JEb) were administered.

In the long-term follow-up period, recurrent disease developed in eleven patients (20%). The diagnosis of original tumor in these 11 patients was made prenatally in 4, at birth in 6 patients, and at the age of 11 in one patient. According to Altman's classification, 2 of these patients were Type II, 5 were Type III, and 4 were Type IV. All of these patients were treated with primary surgery. In 2 patients, chemotherapy was given after the excision of the primary tumor. The pathological results of the original tumors were mature teratoma in 4, immature teratoma in 4, and malignant teratoma in 3 patients (YST). The median follow-up period at recurrence was 29 months (5 months-12 years). Four patients were diagnosed with palpable sacrococcygeal masses by physical examination during routine follow-up. Five cases did not have abnormal signs or symptoms, but serum AFP levels were elevated. In total, the serum levels of AFP were elevated in most of the recurrent patients, but not in all (9/11). Among those with elevated AFP levels, the range was between 5,243 and 58,745. One patient had recurrent urinary infections and the remaining one patient had constipation and weakness in the lower extremity. All of these patients underwent USG and MRI examinations.

Pathological examination revealed malignant relapse with YST in 6 patients (Table III). The recurrence was local in 10 patients, and in one patient, it was combined with distal metastatic lesions in the liver and lungs; all coccyges had been previously removed during the primary surgeries. All 11 recurrent cases received a second operation, and the tumors were removed completely.

The recurrence rate in mature teratomas was 13.1% (5/38) with a 40% malignancy rate while the recurrence rate in immature teratomas was 50% (4/8) with a 75% malignancy rate. The recurrence of mature teratoma after malignant teratoma was detected in one patient (Table IV).

Most of the recurrence occurred in the first 2 years of life (72.7%; 8/11) but the risk of recurrence continues into older ages (12 years in this series) as the recurrence of a mature teratoma at 12 years of age was observed (8).

During this study, one patient with malignant SCT and a recurrence of malignant SCT with distal metastatic lesions died.

We examined the relationship between the clinical characteristics of patients and recurrent tumors in Table V below. Only the pathology of the primary tumor showed a statistically significant relationship (p=0.02).

Table II. Altman's classification of diagnosis and histology after surgery

	Type I	Type II	Type III	Type IV	Total	p value
Mature	15	12	5	6	38 (69.1%)	
Immature	1	2	3	2	8 (14.5%)	0.001
Malignant	0	0	4	5	9 (16.4%)	
Total	16 (29.1%)	14 (25.5%)	12 (21.8%)	13 (23.6%)	55	

Table III. Comparison of Altman's groups

Altman's Type		p value
Type I	Type II	0.742
	Type III	0.001*
	Type IV	0.001*
Type II	Type I	0.742
	Type III	0.005*
	Type IV	0.004*
Type III	Type I	0.001*
	Type II	0.005*
	Type IV	0.981
Type IV	Type I	0.001*
	Type II	0.004*
	Type III	0.981

Table IV. Histology of SCTs at original operation and recurrent operation

Histology before recurrence	Number of patients	Histology after recurrence			Malignant recurrence rate
		Mature	Immature	Malignant	
Mature	38	3	0	2	5% (2/38)
Immature	8	0	1	3	37.5% (3/8)
Malignant	9	1	0	1	11.1% (1/9)
Total	55	4	1	6	10.9% (6/55)

SCTs: Sacrococcygeal teratomas

Table V. The relationships between the malignant recurrence and clinical features

		Number of patients	Number of malignant recurrent patients	p value
Sex	Male	10	2	0.29
	Female	45	4	
Histology before recurrence	Mature	38	2	0.02*
	Immature	8	3	
	Malignant	9	1	
Operation age	0-28 days	33	4	0.72
	28 days-1 year	3	1	
	>1 year	19	1	
Altman's classification	Type I	16	0	0.82
	Type II	14	2	
	Type III	12	3	
	Type IV	13	1	

Discussion

SCT is a rare EGCT mostly diagnosed prenatally, during infancy or in early childhood. Neonatal SCTs are mostly mature but can also contain immature and/or malignant components.

Our study included 55 patients with SC-GCTs treated at our center. The male-to-female ratio was 1 to 4.5, which is lower than rates reported in the literature (1:3-4) (4,13). The predominant occurrence in one gender lacks a definitive explanation.

The prenatal diagnosis detection rates have increased in recent years with the routine use of maternal USG. Fetal MRI can also be used to provide more detailed anatomical information.

In those patients who are not diagnosed prenatally, the most common presenting cause was the finding of a sacral mass, followed by intrapelvic organ compression symptoms such as constipation, frequent urination or difficulty in urination and weakness in the lower extremities causing repetitive falling or an inability to walk in the current series which is compatible with the literature (5).

In our study, 29.1% of the patients were Type I, 25.5% were Type II, 21.8% were Type III and 23.8% were Type IV according to Altman's classification. Type III and Type IV rates were higher in our series than in the literature (14) most probably due to the referral of those complicated cases from other centers.

There are several factors described in the literature which can increase the risk of recurrence after resection: gross or microscopic incomplete resection, failure to respect the coccyx, and tumor rupture or spillage before or during surgery (4). The recurrence rate after mature teratoma was 13.1%, while it was 50% after immature teratoma. Also, the recurrence of malignant teratoma after an immature teratoma was higher (75%; 3/4) compared to mature teratoma. De Backer et al. (15) and Hager et al. (16) showed that incomplete resection is not the only contributing factor accounting for the development of a malignant recurrence. As most SCTs are composed of cells of different origins and differentiation status in a complex histological pattern, overlooking small areas with YST during pathological assessment has been put forward as being a possible explanation for malignant recurrences after teratomas diagnosed initially as mature.

The risk of malignancy increases with age. While most mature and immature teratomas were diagnosed prenatally, at birth, or in the neonatal period, the mean time of diagnosing malignant teratomas was 16 months. This finding supports Biskup et al.'s (17) theory which suggests that mature teratoma cells have the potential to undergo malignant transformation, meaning that a mature SCT which is not resected or not radically resected may eventually present as a somatic type malignancy.

Derikx JP et al. (18) have also suggested the development of YST directly from the teratoma via malignant transformation, while others suggest that microscopic YST foci present in the previous teratoma, if not recognized initially, ultimately predominate in the recurrent tumor (19-21)

The risk of malignancy in Types III and IV according to Altman's classification was higher compared to Types I and II. This finding can be explained by the relatively late diagnosis of those types.

During conventional follow-up, recurrences are detected by physical examination, imaging techniques such as MRI, CT, or US, and the measurement of serum markers. The serum level of AFP (secreted by YST cells) was elevated in most of the recurrent patients, but not in all (9/11). Therefore, serum AFP levels are an important determinant, but alone are not sufficient to diagnose the recurrence of SCTs (in another study, AFP levels had a 75% sensitivity and 96% specificity in diagnosing recurrent patients (22). The history of the patients, the clinical examination findings and the radiologic imaging findings are important in identifying recurrent patients. In our study, MRI was the gold standard diagnostic method.

Recurrent tumors may have a different histopathological type than the original tumor. The risk of recurrence as a malignant tumor after immature teratomas were higher than the mature teratomas (75% vs. 40%); and also, a case of recurrent mature teratoma after malignant teratoma has been reported (4,18).

The most malignant element is the YST. Rarely, these tumors may include another malignant component, usually embryonal carcinoma, or even more rarely a non-germ cell/somatic malignant component such as primitive neuroectodermal tumor (23).

According to our study and the literature (2), most of the recurrent SCTs occur within the first 2 years (in our study 8/11); however, because of the continued risk of recurrence, we recommend following up these patients at least up to the age of 6 years.

In earlier studies of GCTs, the survival of children with SC-GCT was very poor (24,25). This site is no longer considered to be associated with poor survival in more recent reports since the introduction of the platinum-based regimen and progress in surgery (13). In our study, the mortality rate was approximately 1.8% (1/55). In the German review, the only significant prognostic factors in SC-GCT appeared to be the presence of multiorgan distant metastases, but neither stage, extent of metastasis, bone involvement, or serum AFP were identified as prognostic factors (26). Our study is consistent with this finding. During this study, we lost one patient with malignant SCT and a recurrence of malignant SCT with distant metastatic lesions.

Study Limitations

One limitation of the present study was the retrospective nature of the data. Additionally, all procedures were conducted at a single institution, and the number of patients was limited, allowing for descriptive, rather than comparative analyses.

Conclusion

The risk of malignancy increases with age and Altman's Type III and IV. Recurrent tumors may have different histopathological types from the original tumor. The risk of recurrence as a malignant tumor after immature teratomas was higher than for mature teratomas.

Ethics

Ethics Committee Approval: This study was approved by the Ege University Faculty of Medicine, Medical Research Ethics Committee (approval no.: 20-11T/4).

Informed Consent: Informed consent was obtained for all subjects.

Authorship Contributions

Surgical and Medical Practices: Ü.Ç., A.Ç., M.O.E., Concept: M.O.E., Design: S.H., Ü.Ç., M.O.E., Data Collection and/or Processing: S.H., G.S., Analysis or Interpretation: S.H., Ü.Ç., G.S., A.Ç., M.O.E., Literature Search: S.H., Writing: S.H., Ü.Ç.

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