# Multimodal treatment of children with sacrococcygeal yolk sac tumor: retrospective analysis of clinicopathology characteristics and relapse-free survival

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June 1, 2020

Multimodal treatment of children with sacrococcygeal yolk sac tumor: retrospective analysis of clinicopathology characteristics and relapse-free survival

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Running title: Relapse-free survival of sacrococcygeal yolk sac tumor

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List of Abbreviations

| Sun Yat-sen University Cancer Center | SYST |
|---|---|
| relapse-free survival | RFS |
| overall survival rates | OS |
| sacrococcygeal yolk sac tumor | SYST |
| germ cell tumors | GCT |
| alfa fetoprotein | AFP |
| complete remission | CR |
| partial remission | PR |
| extracranial germ cell tumors | EGCTs |
| cyclophosphamide | CTX |
| vinorelbine | NVB |
| International Germ Cell Consensus Classification | IGCCC |

| | |
|---|---|
| Sun Yat-sen University Cancer Center | SYST |
| risk factor | RF |



## ABSTRACT

### Objectives

The aim of the study was to explore the clinicopathological characteristics of sacrococcygeal yolk sac tumor (SYST) associated with relapse.

### Methods:

We collected clinical data regarding patients aged <18 years with SYST treated at Sun Yat-sen University Cancer Center between 2007 and 2018. We investigated prognostic factors of age, stage, initial tumor size, pathological response to neoadjuvant chemotherapy and alfa fetoprotein (AFP) in univariate and multivariate analysis. The Kaplan-Meier method was used to estimate the relapse-free survival (RFS).

### Results:

We enrolled 26 patients with SYST (median age 1.7 years; range, 2 months to 5 years). Patients with predominance of female had elevated AFP at diagnosis (median 50,480 ng/ml, range 1,200-80,300,000). Twelve patients were stage IV. Neoadjuvant chemotherapy was administered to 20 cases. Six patients underwent resection as initial therapy. Resected tumor size at upfront resection was measured $< 4.0\text{cm} \times 3.0\text{cm}$. No patient died of disease at last follow-up. Relapse occurred in 12 patients. Patients with specimen exhibiting no malignant component after chemotherapy didn't experience recurrence. Frequencies of recurrence were once in 5 patients, 3 in 2 patients, 2 in 3 patients, 4 in 1 patient and 6 in 1 patient, respectively. All relapsed patients still achieved partial remission (PR) or complete remission (CR) after salvage therapy. The cohort reached a 5-year RFS of 55.2% (median follow-up 59.5 months; range, 16-155). Univariate analysis identified sex as a significant prognostic factor of RFS ($P = 0.02$). In multivariate Cox regression, no variables had statistically significance. Patients with $> 2$ factors (boy, initial tumor size $> 4\text{cm}\times3\text{cm}$, AFP $> 60{,}000$ ng/ml and poor pathological response) had poor RFS.

### Conclusion:

Sex is a predictive factor of RFS in SYST. Girls with smaller initial tumor size, lower AFP and good pathological response have better RFS. Salvage chemotherapy can benefit patients.

**Keywords: Sacrococcygeal region; Endodermal sinus tumor; Combined modality therapy; Relapse-free survival; Pediatrics**

## Introduction

Germ cell tumors (GCTs) are formed by aberrant migration of primitive germ cells arising in midline sites including brain, head/neck, mediastinum, gonads, retroperitoneum, sacrococcygeal region and vagina. GCTs are classified as gonadal and extragonadal germ cell tumors on the basis of origin. Sacrococcygeal GCT represents approximately 40% of primary extragonadal and extracranial germ cell tumors (EGCTs) among children[1]. Most pediatric tumors stemming from the region are benign teratomas followed by malignant yolk sac tumor (endodermal sinus tumor). Sacrococcygeal yolk sac tumors (SYSTs) are generally characterized by external mass growing around the sacrum and coccyx accompanied by elevation of AFP. A certain proportion of patients still developed local relapse although they received a first-line multidisciplinary treatment. Most of clinical explorations of sacrococcygeal GCT were confined to few case reports. The prognostic factors in relation with sacrococcygeal GCTs were poorly understood.

Here, we studied the relapse-free survival (RFS) rates, prognostic factors, and therapeutic effect of salvage treatment in a retrospective cohort of patients with SYST. Finally, we evaluated the combined prognostic factors of clinical significance on RFS.

## Methods

### Eligibility

All patients aged [?]18 years with newly diagnosed primary SYST at SYSUCC between January 2007 and December 2018 were eligible. Initial diagnosis was established on the basis of confirmed histology and AFP exceeding age-related normal range. The staging was performed according to classification system developed by Children's Oncology Group (Supplement 1). Clinical variables were recorded regarding age, sex, AFP level, stage, metastasis site, primary tumor size, treatment and pathological response. The date of last follow-up was April 18, 2020. In the cohort, initial treatment decision was made according to tumor size, stage and risks by treating physician. The present study was approved by the Ethics Board of the Sun Yat-sen University Cancer Center (SYSUCC, 2020-FXY-115) and conducted in accordance with the Helsinki Declaration.

### Chemotherapy and evaluation

Preoperative courses of chemotherapy were administered to patients with bulky disease or metastasis. Initial chemotherapy comprised cisplatin, etoposide, and bleomycin (PEB regimen): bleomycin 15 mg/m$^2$ on day 1, etoposide 100 mg/m$^2$on days 1 through 5 and cisplatin 20mg/m$^2$ on days 1 through 5. Every cycle was repeated at three-week interval. Chemotherapy doses were adjusted for infants $<$ 12 months of age: cisplatin 0.7 mg/kg/dose, etoposide 3 mg/kg/dose, and bleomycin 0.5 mg/kg/dose.

AFP was monitored prior to every cycle of chemotherapy. Patients underwent a thorough evaluation every two cycles of chemotherapy by imaging work-up and tumor marker determinations. We proposed 4-6 preoperative chemotherapy courses before a radical complete resection without major morbidity was achieved. Postsurgical chemotherapy was determined based on histologic findings. If the resected specimen showed no viable tumor cells and AFP declined within reasonable range of half-life, pathologic response was considered complete. Additional two courses of chemotherapy were administered to patients. Patients with malignant residual disease in pathological specimen continued to receive chemotherapy. Patients with progressive disease or no response to the initial chemotherapy were considered treatment failures and received second-line chemotherapy. Total cycles of chemotherapy varied between 6-8 courses.

### Tumor resection

Patients unable to receive complete resection or at high risk of rupture underwent biopsy prior to treatment. Tumor resection was considered when primary tumor shrank approximate to 2cm x 3cm to minimize risk of rupture or spillage during resection. Tumor resection field included the tumor pseudocapsule and en-bloc coccyx bone as possible. Tumors were resected in toto without proof of rupture as possible as surgeons could[2].

### Salvage therapy after relapse

Therapeutic approach for patients with recurrent SYST was not homogeneous. Therapeutic strategies were developed based on the response to the previous treatment. The salvage strategy consisted of platinum-based chemotherapy basically followed by resection of residual masses when possible. External-beam irradiation was performed in patients with recurrent local relapse at the dose of 50 Gy. Oral cyclophosphamide (CTX) and vinorelbine (NVB)-containing maintenance regimens or VP16 alone were administered to repeated relapsed patients with inoperable residual disease after salvage chemotherapy or residual disease after resection. Schedule was as following: CTX 50 mg/m$^2$, d1-28; NVB 25 mg/m$^2$, on days 1, 8, 15 or oral etoposide 50 mg/m$^2$, d1-14, two weeks break meaning two weeks on and two weeks off. Each cycle of treatment was repeated every 4 weeks.

### Statistical analysis

Statistical analysis was conducted using the statistical software SPSS 25 (IBM Corp., Armonk, NY). Chi-square test was used to analyze the associations between pathological response and patient characteristics. Complete remission was considered as normal serum tumor markers ($<$10 mg/L or below the age-related

reference value) and absence of all imaging abnormalities in computed tomography or magnetic nuclear resonance imaging. Partial remission was defined as AFP decline and shrinkage of tumor size by at least 50%. Relapse was defined as detection of new lesions in local or distant sites in terms of complete remission. The RFS were generated according to the Kaplan and Meier method. The influences of suspected prognostic factors associated with RFS were analyzed with the Breslow test due to most relapse occurring in short time. Log-rank test was performed to determine the survival difference in long term. RFS was calculated as the time from diagnosis to the first relapse or death (death related with disease or therapy-oriented complication) or from the first relapse to the next relapse. All statistical tests were two-sided and the $P$ values $< 0.05$ were considered statistically significant.

## Results

### Patient demographics

In total, 26 eligible patients were enrolled with SYST onto the present study between March 2008 and November 2018, representing 20.6% of total 126 germ cell tumor diagnoses in the period. Patient characteristics were listed in Table1. Briefly, patients had a median age of 1.7 years (range, new born to 5 years). The male to female ratio was 11:15. The median AFP levels were 50,480 mg/L (range, 1,200-8,0300,000 mg/L) at diagnosis. The stage distribution was 3 patients with stage II, 11 with stage III, and 12 with stage IV tumors. In patients with stage IV, metastatic sites were lung alone in 6 cases, bone and lung in 3 cases, liver and lung in 2 cases and liver alone in 1 case (Table 1).

### Treatment and response

Upfront surgery was undergone in 6 (23.1%) patients: stage II in 1 case, stage III in 4 cases and stage IV in 1 case (unknown the pathological diagnosis). Tumor size (defined as the greatest extent measured by MRI scan) was measured [?]4cmx3cm. Four patients achieved CR and 2 patients had PR after resection. The median of chemotherapy cycles after resection was 4 (range, 4-6). Twenty (76.9%) patients with initial tumor size >4cmx3cm received a median of 4 courses (range, 2-8) neoadjuvant chemotherapy as first line treatment (Table 1). Primary tumor shrank approximate to 2cmx3cm and AFP declined to <100ng/ml prior to surgery.

Histopathology after neoadjuvant chemotherapy was notable for nonviable cells in nine patients. None of them developed relapse. Among the remaining 11 cases with confirmed malignant disease, 4 patients had no relapse and 7 patients experienced relapse.

To evaluate assumed prognostic parameters in pathological response to neoadjuvant chemotherapy, we compared sex, age, AFP level, stage at diagnosis, number of neoadjuvant chemotherapy cycles and relapse between good and poor responders. In this analysis, these variables were comparable for both groups (Table 2).

### Survival

No patients died of relapse and therapy-associated complications at last follow-up. Twelve patients developed relapses. Total frequencies of recurrence were once in 5 patients, 2 in 3 patients, 3 in 2 patients, 4 in 1 patient and 6 in 1 patient respectively (Table 1). Among these, 11 patients developed local relapse (42.3%) and one patient displayed a distant relapse at right cerebral parietal lobe.

The five-year overall survival (OS) and RFS rates of the whole cohort were 100.0% and 55.2% with a median follow-up of 59.5 months (range, 16-155 months, Figure 1). The estimated 5-year RFS rates for stage III and stage IV were 50.9% and 62.5%, respectively (P = 0.40). There was a trend towards better 5-year RFS for girls (64.2% +- 17.6%) compared with boys (40.0% +- 15.5%) (P = 0.02). The RFS between the two age groups([?]2 years vs >2 years) was not significantly different(P = 0.82)(Table 3). Regarding AFP level, the 5-year RFS rate was 56.3% for [?]60,000ng/ml, and this rate was higher than for >60,000 ng/ml (P = 0.91; Table 3). The 5-year RFS of patients with poor pathological response was impaired as compared with

good pathological response (38.7% +- 13.0%; 11 of 20 patients versus 100%; 9 of 20 patients; P = 0.03). No risk factors were considered prognostically unfavorable in multivariate analysis.

Although no variables except gender were significantly associated with RFS (Table 2), good pathological responders, smaller initial tumor size and lower AFP level represented favorable prognostic factors in terms of RFS. Based on clinical significance of these three factors in combination with gender, the sum of the points(adverse factors: male or poor pathological responder or initial tumor size greater than 4.0 cmx3.0 cm or AFP >60000ng/ml) allotted correlated with the following risk groups: groupI($n$ = 11, 55.0%), 0-2 adverse factors; group II ($n$ = 9, 45.0%), 3-4 adverse factors. Table 4 showed two patients developed relapse in groupIand five patients had relapse in groupII. Seven patients were in alive after salvage therapy. Boys accounted predominantly in group II that might be responsible for the significant difference. We excluded sex in further analysis and stratified the cohort into two groups according to initial tumor size, pathological responders and AFP level. No relapse was observed in groupIwith 0-1 adverse risk factor. Seven patients developed relapse in group II with 2-3 adverse risk factors (P = 0.07, Table 5).

**Salvage treatment after relapse**

Resection and chemotherapy represented the cornerstone of salvage treatment. All 12 relapsed patients underwent the second-line carboplatinum-based chemotherapy. Other chemotherapy protocols contained docetaxel/vinorelbine, paclitaxel/nedaplatin and high-dose paclitaxel/ifosfamide/cisplatin. Patients with local relapse underwent resection. Two patients with recurrent relapse received a total irradiation dose at 50 Gy[3]. Complete response was achieved in 8 patients. Four patients had partial response.

**Second neoplasm**

One patient with two years old at initial diagnosis, who relapsed twice and prolonged maintenance treatment containing etoposide on her guardian's own will, developed osteosarcoma.

**Discussion**

GCTs represent a heterogenous group of tumors originating from primitive germ cells distributed in sexual gland and the midline sites. Malignant germ cell tumors (MGCT) are rare and constitute approximately 2% of all malignant tumors in children[4]. The insight into etiology and pathogenesis of pediatric GCTs is still limited. Sacrococcygeal GCTs may be caused by apoptosis-related pathways and associated with polymorphisms in BAK1[5]. Pediatric extracranial GCTs are divided into three subtypes: teratomas, malignant GCTs and mixed GCT. Furthermore, malignant GCTs include seminomatous and nonseminomatous GCT. Teratoma is one of the most frequent benign tumors occurring in sacrococcygeal region in young children followed by yolk sac tumor (YST), namely endodermal sinus tumor [6]. According to limited data in our study, children developing SYST were very young (median age 1.7 years) and girls were more likely to develop SYSTs than boys similar with sacrococcygeal teratomas[7].

More literatures were reported regarding sacrococcygeal teratomas than YSTs. The SYSTs presented a mass either protruding outward from the buttocks from the tip of the sacrum, or impalpable mass within the pelvic cavity compressing the bladder or rectum consistent with teratoma[8]. Unlike teratoma, YSTs secret AFP and serum half-life of AFP is 5 to 7 days. Elevated serum AFP levels above age-related normal range can be viewed as a dynamic tumor marker to assist diagnosis and monitor response to treatment. Interestingly we observed AFP would show a transient elevation in one week after initial chemotherapy, however, AFP would decline to lower extent near to next cycle in most patients. Metastasis occurred in 46.2% patients at diagnosis demonstrating that SYSTs were highly aggressive tumor[9] . Liver, lung and bones were more frequent metastatic sites. The other rare distant metastatic site including brain was also seen in one patient.

A multimodal approach in management of sacrococcygeal tumors was recommended because of larger tumor size and advanced stage at presentation as literature reported that malignant sacrococcygeal tumors were usually very advanced at diagnosis and metastases were present in 50% of patients[9]. SYSTs are highly sensitive to chemotherapy. Cisplatin-based chemotherapy has significantly improved outcomes for most children with extracranial GCTs. Platinum-containing chemotherapy with cisplatin, etoposide, and

bleomycin (PEB) is recommended as first-line chemotherapy. After a median of four cycles of preoperative chemotherapy followed by delayed tumor resection, the modality may facilitate complete surgical resection in the setting of avoiding rupture. However, more cycles of chemotherapy administered didn't seem to benefit surgical resection for surgeons because of high chemotherapy sensitivity resulting in no definite tumor margin left. Chemotherapy after incomplete resection has the benefit for survival, however, complete resection of the coccyx is still the basic principle[2,10].

Although the overall survival of SYST tumor was optimal, the RFS remained still low. Literature reported the 5-year survival rate was 56.9% for sacrococcygeal tumors in the past [11]. In our analysis the 5-year RFS rate was 55.2%. The pediatric investigation on a small number of patients identified sacrococcygeal tumors as high risk[12]. Furthermore, the inferior outcome has been attributed to delayed diagnosis and incomplete resection at the time of original surgery[13].

We conducted a retrospective cohort study investigating the prognostic factors related with relapse. Boys were at higher risk of early relapse in univariate analysis. An International Collaborative study also showed boys (aged 11 years and older) with International Germ Cell Consensus Classification (IGCCC) intermediate-risk or poor-risk features had inferior outcomes[14]. Metastasis didn't play a significant role in the outcome of children with advanced stage. This may be explained that high chemo-sensitivity of YST could achieve durable complete remission of metastasis. Literature reported risk factors associated with recurrence included gross or microscopic incomplete resection, unresected coccyx, tumor rupture or spillage before or during surgery[15]. However, some risk factors were still under controversy[16]. Although initial tumor size, AFP level and pathological response did not show statistical differences in univariate analysis, we could not preclude that these were acknowledged factors associated with prognosis clinically. We selected the three clinical significance variables combined with sex to classify the patients into two groups as following: Group I with 0-2 adverse factors and Group II with 3-4 adverse factors. The RFS difference between the two groups was significant in analysis. We speculated that higher AFP level represented higher tumor burden, greater initial tumor size resulted in increasing difficulty in complete resection and poor pathological response may lead to microscopic residuals. Boys tended to present larger tumor size at diagnosis and have poor pathological response to neoadjuvant chemotherapy. This hypothesis requires more evidence to support.

Salvage therapy could still benefit patients when patients relapsed. Patients were still sensitive to second-line chemotherapy of other platinum-based or paclitaxel-containing protocols. Salvage chemotherapy was able to facilitate completeness of relapse tumor resection. We also explored low-dose oral CTX and NVB or etoposide containing chemotherapy as maintenance therapy in recurrent relapsed patients without overt disease in terms of slight elevation of AFP. One patient didn't follow the doctor's instructions strictly and prolonged maintenance therapy for two years. The patient developed osteosarcoma and is receiving the chemotherapy for second neoplasm.

Some limitations of our study lied in its retrospective character and small sample size. The experience of surgeons had impact on the decision making. Multicenter prospective studies are needed to determine prognostic factors in large sample groups.

In conclusion, the present study demonstrated SYSTs occurred more frequently in young children and RFS of pediatric SYSTs remained still low awaiting multidisciplinary effort. Salvage therapy can benefit the survival. Male had inferior RFS. Greater initial tumor size, poor pathological response to neoadjuvant chemotherapy and higher AFP level in combination of male gender had negative impact on RFS.

**Acknowledgments**

We thank the staff in department of Pediatric Surgery, the first affiliated hospital of Sun Yat-Sen University for surgical support and Chunmei Chen for developing the study database.

**Conflicts of interest**

All the authors declare that they have no conflicts of interest.

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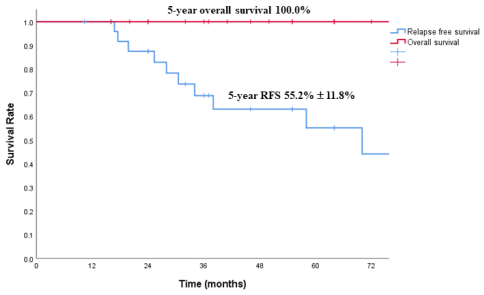


FIGURE 1 Kaplan-Meier estimates of 5-year survival of the sacrococcygeal yolk sac tumor: red line overall survival 100%; blueline 55.2%±11.8% [n=26]

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