Clinical Outcomes of Extracranial Germ Cell Tumors: A Single Institute's Experience

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ABSTRACT

Objective: To determine the clinical features and treatment outcomes of pediatric extracranial germ cell tumor (EGCT) in Thailand.

Materials and Methods: A retrospective chart review of children under 15 years old with newly diagnosed EGCT who were treated at Faculty of Medicine Siriraj Hospital from January, 2004 to December, 2013 was conducted.

Results: Forty-four patients were included in the study. The median age at diagnosis was 1.74 years (1 day-14.7 years) with the median follow up time of 6.9 years (14 days-15.2 years). Twenty-eight patients (64%) had extragonadal tumor. The most common primary tumor location was the sacrococcygeal area. Majority of the patients (61%) had malignant EGCT; yolk sac tumor was the most common diagnosis. Six patients (14%) had stage IV disease. Forty patients (91%) underwent surgery; 27 patients (61%) received chemotherapy. Thirty-eight patients (86%) achieved remission; 3 patients (7%) subsequently relapsed at a median time of 1 year. Eight patients (18%) died, mostly from tumor progression. The 5-year event-free survival (EFS) and overall survival (OS) rate were 78.3% and 81.1%, respectively. Patients achieving total tumor removal had significantly better 5-year EFS and OS. Cox regression analysis revealed that the adequacy of surgery was the only prognostic factor for survival.

Conclusion: The survival rate of pediatric EGCT in our study was relatively favorable, but still inferior to that of developed countries. Novel therapy may be warranted for those patients who are unresponsive to the current treatment.

Keywords: Extracranial germ cell tumor, EGCT, survival rate, treatment outcome, Thailand (Siriraj Med J 2021; 73: 680-686)

INTRODUCTION

Germ cell tumor (GCT) is a rare tumor, accounting for 3% of childhood cancers.[1] Extracranial germ cell tumor (EGCT) is more common than intracranial germ cell tumor (IGCT), and more than half of EGCT was extragonadal in origin[1]. EGCT can be classified based on histological features into 2 categories: teratoma and malignant GCT. The clinical manifestations are varied, depending on the location of the tumor. EGCT is found to be associated with several genetic syndromes causing gonadal dysgenesis such as Klinefelter syndrome, Turner syndrome, and Swyer syndrome.[2-4] Those with EGCT appear to respond well to the treatment and can attain long term remission. The mainstay of treatment of EGCT is surgery, although chemotherapy may be beneficial in some cases which harbor a malignant component. The

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outcome of EGCT in developed countries was relatively favorable.[5] Previous study in Thailand demonstrated the 5-year overall survival (OS) rate of pediatric germ cell tumor (GCT) of 70.6%; however, this study included both IGCT and EGCT.[6] The clinical information regarding Thai patients with EGCT has been scarce. Our study aimed to determine the clinical features and outcomes of pediatric EGCT in one of the tertiary centers in Thailand.

MATERIALS AND METHODS

This retrospective study was conducted in patients diagnosed with EGCT at the Department of Pediatrics, Faculty of Medicine Siriraj Hospital, from January 2004 to December 2013. All patients with newly diagnosed EGCT during the study period were recruited; those who refuse the treatment were further excluded. The diagnosis of EGCT was established based on clinical features, tumor markers, and radiographic findings. Patients who had normal serum tumor markers must have a histopathology result to confirm a diagnosis of EGCT. The clinical staging of testicular, ovarian, and extragonadal GCT was determined by the Children's Oncology Group staging system.[7,8] Surgery was a primary treatment for resectable tumors. Those who had an unresectable tumor received neoadjuvant chemotherapy consisting of cisplatin, etoposide, and bleomycin (PEB) before surgery.[9] Patients with teratoma were treated with surgery solely. However, those children with immature teratoma (IT) either greater than stage II or grade III tumor may have received PEB upon physician discretions. Among patients with nonteratomatous EGCT, those with stage I testicular GCT did not receive adjuvant chemotherapy after surgery, while other patients were subsequently treated with adjuvant PEB. The responses to the treatment were classified using RECIST guidelines.[10] This retrospective study was approved by the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (Si 380/2020).

Statistical analysis

The collected data were analyzed using SPSS Statistic version 22.0 for Windows (SPSS Inc., Chicago, IL). Demographic data were described using mean, medians, and percentage. The Kaplan-Meier survival curve was used to demonstrate the OS and event-free survival (EFS) rate of EGCT patients; event was defined as tumor relapse or death. The patients' age at diagnosis, stage, histopathology subtype, site of tumor, and adequacy of surgery were analyzed using the Cox regression analysis to determine the predictors of survival. The adjusted hazard ratio (HR) and 95% confidence intervals (CIs) were calculated. A p-value of <0.05 was regarded as being statistically significant.

RESULTS

Forty-seven patients were diagnosed with EGCT; 3 patients were excluded due to treatment refusal. There were 44 patients included in this study, with the median age at diagnosis of 1.74 years (range 1 day-14.7 year). Twenty-eight patients (64%) had extragonadal tumor; sacrococcygeal area was the most common primary tumor location. Majority of the patients (61%) had malignant EGCT. Yolk sac tumor (YST) was the most common histopathological diagnosis, followed by mature teratoma (MT) and mixed GCT. Of all 10 patients with mixed GCT, MT with a component of YST was the most common diagnosis. The demographic data, clinical features, histopathology and staging of EGCT are presented in Table 1. Three patients had underlying genetic diseases, including 1 Down syndrome (DS) with stage I retroperitoneal IT grade II, 1 DS with stage I ovarian dysgerminoma, and 1 Cornelia de Lange syndrome (CdLS) with stage III sacrococcygeal mixed GCT comprising of MT and YST.

One patient presented with hemophagocytic lymphohistiocytosis (HLH) and subsequently diagnosed with mediastinal germinoma. He ultimately died of infectious complication before receiving treatment for EGCT. Thirty patients (68%) were treated with upfront surgery while 13 patients (29%) received chemotherapy as an initial treatment. Of all 30 patients undergoing upfront surgery, 16 patients did not receive adjuvant chemotherapy since their tumors were completely resected and contained no malignant component. Twenty-four patients (55%) received combination treatment of surgery and chemotherapy, while 16 patients (36%) were solely treated with surgery and 3 patients (7%) received chemotherapy without surgical treatment (Fig 1). Chemotherapy (PEB) was prescribed for 27 patients, including 26 patients with malignant EGCT and 1 patient who had sacrococcygeal IT grade III with lymph node metastasis.

Three patients with a pathological diagnosis of sacrococcygeal IT grade II (1 patient) and III (2 patients) had elevated serum tumor markers, but did not receive chemotherapy. All of them were alive and free of disease at the end of the study.

One patient died before the treatment of EGCT was initiated. Thirty-eight patients (86%) had a complete response; 5 patients who were unresponsive to treatment subsequently died of disease. Relapse occurred in 3

TABLE 1. Demographic data, histopathology and staging of all patients (n=44).

Characteristics		Number (%)
Gender	Male	18 (41)
	Female	26 (59)
Primary site of tumor	Sacrococcygeal area	12 (27)
	Ovary	11 (25)
	Retroperitoneum	6 (14)
	Mediastinum	6 (14)
	Testis	5 (11)
	Mandible	1 (2)
	Bladder	1 (2)
	Vaginal wall	1 (2)
	Stomach	1 (2)
Histopathology results	Teratoma	
	-IT	12 (27)
	-MT	5 (11)
	Malignant germ cell tumor	
	-YST	13 (29)
	-Germinoma	4 (9)
	-Mixed germ cell tumor	
	-MT with YST	5 (11)
	-IT with YST with choriocarcinoma	3 (7)
	-IT with YST	1 (2)
	-Germinoma with choriocarcinoma	1 (2)
Staging	I	17 (39)
	II	3 (7)
	III	18 (41)
	IV	6 (14)

Abbreviations: IT, immature teratoma; MT, mature teratoma; YST, yolk sac tumor

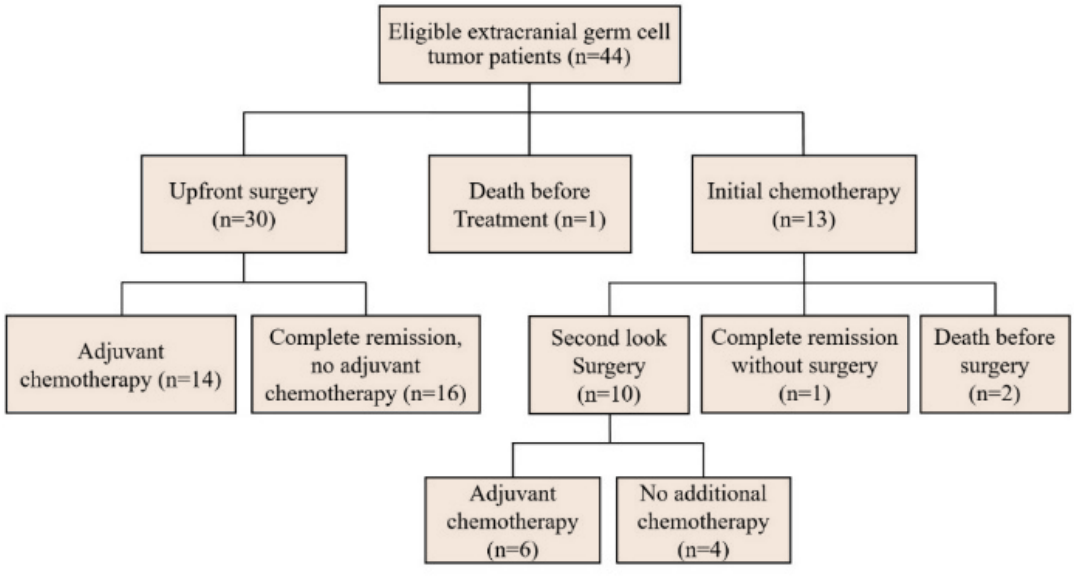

Fig 1. Treatment of patients with extracranial germ cell tumor.

patients, with a median time to relapse of 1 year (range 3.3 months-1.1 years). Of all 3 patients with relapse, 2 patients (1 patient with YST at vaginal wall and the other with IT at mandible) achieved remission after a combination of surgery and chemotherapy, and 1 patient died of disease progression. The mortality of EGCT in this study is detailed in Table 2. Among 27 patients who received chemotherapy, 19 patients (70%) experienced treatment-related toxicity. The most common adverse reaction from chemotherapy were infection (55%) and hematotoxicity (55%), followed by renal toxicity (37%). Two patients with mediastinal mixed GCT had concomitant hematologic malignancies. One of them developed prolonged cytopenias during treatment; his bone marrow aspiration result was compatible with acute megakaryoblastic leukemia. The other patient had tumor progression and subsequently died of disease; the autopsy result revealed a component of myeloid sarcoma within the remaining mediastinal mass with the presence of isochromosome 12p abnormality.

The 5-year EFS and OS were 78.3% (95%CI 10.3-13.9) and 81.1% (95%CI 10.8-14.2), respectively (Fig 2). The median follow-up time was 6.9 years (range 14 days-15.2 years). The comparison of EFS and OS according to clinical factors is demonstrated in Table 3. Cox regression analysis was performed to determine the predictors of mortality; the only factor associated with survival was the adequacy of surgery (HR 8.69, 95% CI 1.44-52.26, *p*-value 0.018).

DISCUSSION

In our study, EGCT was common among patients under 2 years of age, with a female preponderance; this was concordant with other studies.[1,11] Sacrococcygeal area appeared to be the most common primary site, which corresponds with a previous study.[11]

Klinefelter syndrome, Turner syndrome, and Swyer syndrome were found to be associated with EGCT[2-4] but none of the patients in our study harbor those conditions. However, 3 of our patients had underlying genetic diseases including DS and CdLS. Individuals with DS have been reported to have EGCT, but the incidence of EGCT in DS was relatively low compared to that of hematologic malignancies.[12] CdLS is a rare syndrome resulting from mutation in cohesin protein[13], and typically affected craniofacial, gastrointestinal and central nervous systems. Although mutation of cohesin might be associated with the development of cancer, there was no clear evidence that CdLS increased the risk of cancer. Few case reports of CdLS with Wilms tumor and liver hemangioendothelioma have been documented[14], but there was still no report of EGCT in CdLS. Hence, we believe that the finding of EGCT in CdLS in our study might be an incidental finding.

TABLE 2. Mortality of extracranial germ cell tumor patients (n=8).

Patient	Diagnosis	Stage	Treatment	Response of treatment	Cause of death
1	DS with retroperitoneal IT grade II	I	TTR	CR	Infection (not related to cancer treatment)
2	Mediastinal IT grade III	I	TTR	CR, then relapse	Disease progression due to treatment refusal
3	Sacrococcygeal IT grade III	III	TTR with CMT	PD	Disease progression
4	Mediastinal germinoma	III	None	Not evaluable	HLH
5	Mediastinal mixed GCT	III	CMT with TTR	PR	Disease progression
6	Mediastinal mixed GCT	III	CMT	PR, concomitant myeloid sarcoma	Disease progression
7	Mediastinal mixed GCT	III	CMT	PD, concomitant AML	Disease progression
8	Sacrococcygeal YST	IV	CMT	PD	Disease progression

Abbreviations: AML, acute myeloid leukemia; CR, complete response; DS, Down syndrome; GCT, germ cell tumor; HLH, hemophagocytic lymphohistiocytosis; IT, immature teratoma; PD, progressive disease; PR, partial response, TTR, total tumor removal; YST, yolk sac tumor

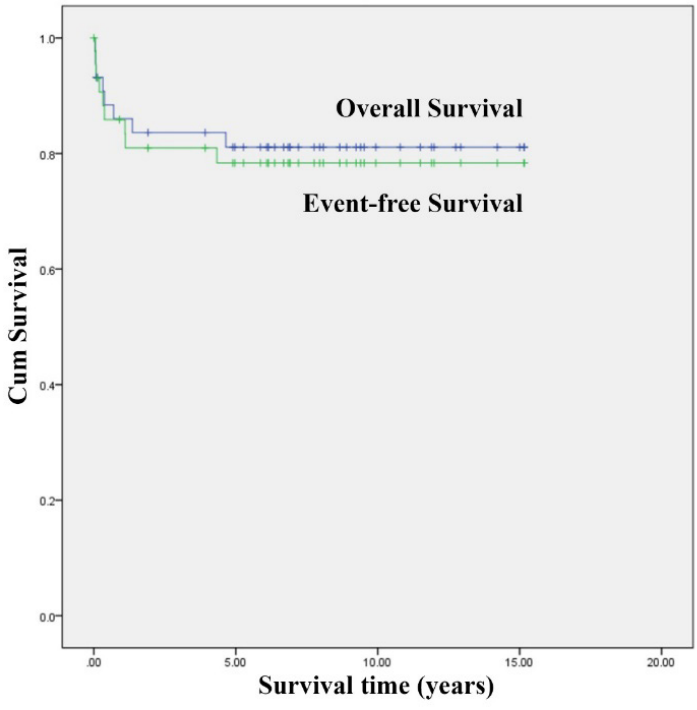

Fig 2. The 5-year event-free survival and overall survival rate of patients with extracranial germ cell tumor.

TABLE 3. Comparison of survival rates according to various clinical factors.

Factors	5-year EFS	*p*-value	5-year OS	*p*-value
Age group at diagnosis				
<11 yr (n=33)	83.8	0.088	87.4	0.056
≥11 yr (n=11)	61.4		61.4	
Site of tumor				
Gonadal (n=16)	100	0.170	100	0.203
Extragonadal (n=28)	65.9		70.5	
Diagnosis				
Teratoma (n=17)	73.7	0.614	80.7	0.961
Malignant germ cell tumor (n=27)	81.1		81.3	
Stage				
I (n=17)	80	0.861	86.7	0.723
II (n=3)	100		100	
III (n=18)	72.2		72.2	
IV (n=6)	80		80	
Adequacy of surgery				
Partial tumor removal (n=3)	33.3	0.023	33.3	0.018
Total tumor removal (n=37)	88.6		91.6	

Abbreviations: EFS, event-free survival; OS, overall survival

Several type of hematologic malignancies, especially acute megakaryoblastic leumemia, were reported in patients with mediastinal GCT.[9,15] Isochromosome 12p might be responsible for the concomitant hematologic malignancies in these patients.[16] Although only one of our patients harbor this abnormal chromosome, we believed that the hematologic malignancies in both of them were related to the mediastinal GCT rather than a secondary malignancy related to cancer treatment since theirs myeloid neoplasms developed very early after the initiation of chemotherapy.

Chemotherapy treatment in IT is controversial, especially in ovarian IT.[17] However, several reports have revealed that chemotherapy might not benefit for other IT patients, even if they have malignant foci or elevated tumor markers.[18,19] In accordance with the aforementioned studies, all 3 IT patients with elevated serum tumor markers in our study survived after having a solely surgical intervention.

Previous reports revealed that teratoma usually had a better outcome than malignant EGCT.[20] In contrast, patients with teratomatous EGCT in our study had an inferior survival rate compared to malignant EGCT, but without statistical significance. However, other factors, such as treatment abandonment or a patient's preexisting conditions, might have affected the treatment outcome. Among the 3 teratomatous EGCT patients who died in this study, only 1 patient died of a refractory disease, while another patient died of disease progression due to treatment refusal and the other patient with DS died of infection not related to cancer treatment several months after completing therapy.

The 5-year OS rate of 81.1% in this cohort was comparatively favorable to 70.6% of the previous Thai study.[6] However, the aforementioned study included both IGCT and EGCT; the interpretation should be cautious. Improvements in supportive care may account for the better outcome in our study, given the fact that the chemotherapy protocol has not drastically changed. The outcome of present study was inferior to that of developed countries[5]; this may be due to the higher proportion of teratomatous EGCT in that study compared to our study, 78.7% versus 38.6%.

The survival rate of advanced-stage disease was still inferior to early-stage disease[5], including the results of our study. Although several treatment approaches, such as an intensive dose of PEB[21] and high dose chemotherapy with autologous stem cell rescue[22] were initiated in patients with advanced disease, they failed to demonstrate any survival benefit. In addition, disease progression was the major cause of death in our study especially in patients with advanced stage. More effective treatment approaches may be required for such patients. Younger age at diagnosis i.e. less than 11 years old and gonadal tumor in origin were also reported to be a good predictor for survival.[23] Both groups also provided the better survival in our study but without statistical significance, a larger sample size might be needed to better determine the prognostic factors.

A few patients with relapse can be salvaged by surgery. The Cox regression analysis in our study also demonstrated that surgery significantly improved the survival rate. Therefore, for patients whose tumor cannot be completely removed, repeated surgery may be warranted.

There were limitations in this study that need to be mentioned. First, as is common with retrospective studies, some data might be missing or incomplete. Secondly, the sample size in this cohort appears to be small; some significant prognostic factors might be not salient. Thirdly, our center often receives complicated cases, possibly limiting the generalizability of our data and findings.

CONCLUSION

The outcome of EGCT in this study seemed to be favorable but still inferior to that of developed countries, possibly due to the higher proportion of nonteratomatous EGCT in our study. The adequacy of surgery appeared to be factor-associated with better clinical outcomes, whereas novel therapy may be warranted for those patients who are unresponsive to the current treatment.

Conflict of interest: The authors have no conflicts of interest to declare.

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