RESEARCH ARTICLE

Editorial Process: Submission:01/12/2025 Acceptance:07/08/2025

Factors Associated with Survival in Pediatric Extracranial Germ Cell Tumors: A Study Focusing on Postoperative Alpha-Fetoprotein

Sasabong Tiyaamornwong[1], Polathep Vichitkunakorn[2], Pornpun Sripornsawan[3], Pongsakorn Choochuen[4], Chayut Pongpanit[5], Kulpreeya Sirichamratsakul[1], Surasak Sangkhathat[1,4]*

Abstract

Background: Alpha-fetoprotein (AFP) is commonly used in the management of pediatric extracranial germ cell tumors (eGCT), but its prognostic role remains unclear. We investigated survival outcomes and the impact of serial AFP changes after surgery. **Method:** We analyzed data from 129 pediatric eGCT patients (age 0-15) who underwent surgery at our institution. We evaluated overall survival (OS) and recurrence-free survival (RFS). in non-benign eGCTs, serial AFP measurements were performed postoperatively. **Results:** OS and RFS were 87.4% and 82.6%, respectively. Poorer survival was associated with male sex, non-sacrococcygeal extragonadal site, yolk sac tumor/choriocarcinoma histology, initial AFP > 50,000 ng/mL, and operative complications. Postoperative log-AFP values showed significant differences between long-term survivors and non-survivors from one month onwards. AFP normalization (<100 ng/mL) at one month was associated with improved 5-year OS (93.4% vs. 69.4%, p=0.031). **Conclusion:** Serial AFP measurement from one month post-surgery has prognostic value in pediatric eGCT. Patients who fail to normalize AFP should be closely monitored for recurrence.

Keywords: Germ cell tumors- alpha-fetoprotein- teratoma

Asian Pac J Cancer Prev, **26 (7)**, 2489-2497

Introduction

Pediatric extracranial germ cell tumors (eGCTs) are rare neoplasms originating from primordial germ cells in various anatomical locations outside the central nervous system [1]. eGCTs account for approximately 3.5% of childhood tumors, with an incidence of 2.4 new diagnoses per million children per year [2]. About 20% of these are malignant [3, 4]. eGCTs are classified by their primary location and histological patterns. Based on location, they are categorized into gonadal (ovarian and testicular) and extragonadal (retroperitoneal, sacrococcygeal, mediastinal, and vaginal) germ cell tumors [5]. Sacrococcygeal teratoma is the most common extragonadal eGCT, usually presented in the neonatal period [1]. Histologically, eGCTs are classified into mature teratoma (benign), immature teratoma, and malignant eGCTs. Endodermal sinus tumors (yolk sac tumors) and malignant teratoma are common malignant eGCTs in children. Alpha-fetoprotein (AFP) is a serum marker for malignant eGCTs and some teratomas with immature components. Despite advances in multimodal treatment approaches (surgery, chemotherapy, and radiation therapy), a significant proportion of children with eGCTs experience disease relapse or progression, leading to poor survival outcomes [6, 7]. High-dose chemotherapy and autologous blood stem cell transplantation is an active research area for refractory GCT [8, 9].

The primary treatment for eGCTs is complete surgical resection, which is feasible in most cases [7, 10]. However, for patients with large tumors that preclude safe primary resection, neoadjuvant chemotherapy is indicated. The current standard chemotherapy regimen, recommended by the Children's Oncology Group (COG), consists of cisplatin, etoposide, and bleomycin (PEB). Recent studies demonstrate encouraging long-term survival rates for children with malignant eGCTs, ranging from 85% to 95% across all extracranial sites [11]. Despite these promising

*[1]Department of pediatric surgery, Faculty of Prince of Songkla university, Thailand. [2]Department of Surgery, Faculty of Medicine, Prince of Songkla University, Hatyai, Songkla, Thailand. [3]Division of Pediatric Oncology, Faculty of Medicine, Prince of Songkla University, Hatyai, Songkla, Thailand. [4]Department of Biomedical sciences, Faculty of Medicine, Prince of Songkla University, Thailand. [5]Division of Gynecologic Oncology Unit Department of Obstetrics and Gynecology Faculty of Medicine, Prince of Songkla University Hat Yai, Songkla, Thailand. *For Correspondence: surasak.sa@psu.ac.th*

survival rates, the clinicopathological factors associated with eGCT survival remain controversial. While benign eGCTs generally have an excellent prognosis, cases of relapse and malignant transformation years after treatment have been reported [6]. Alpha-fetoprotein (AFP) has been investigated as a potential prognostic marker in various studies, with some demonstrating a correlation between AFP levels and survival outcomes [12-16]. However, recent research has failed to validate the prognostic value of initial AFP levels or immediate postoperative AFP values [14]. This discrepancy raises questions about the optimal timing of AFP evaluation for meaningful prognostic assessment.

Previous studies have explored potential prognostic factors, such as patient demographics, tumor characteristics (histology, stage, site), and treatment modalities [17, 18]. However, the heterogeneity of eGCTs and limited sample sizes in individual studies have hindered the identification of definitive prognostic markers. This study aimed to evaluate the 5-year overall survival (OS) and 5-year recurrent-free survival (RFS) of pediatric eGCTs treated in a tertiary care university hospital in Thailand and analyze factors associated with their survival in our cases, especially the prognostic values of AFP.

Materials and Methods

This study included 169 patients aged under 15 years who were diagnosed with eGCTs and were treated in Songklanagarind Hospital, Thailand, from 1993 to 2023. Thirty-three patients were excluded from the analysis because they had undergone surgery from other hospitals, and seven patients were excluded due to incomplete treatment, giving 129 patients for the outcome analysis. Patients' data, including demographic data, primary tumor site, initial AFP, histopathology, co-morbidity, stage, operative complication, and post-treatment outcomes, were collected retrospectively from the electronic medical record. The study was approved by the Human Research Ethics Committee of the Faculty of Medicine, Prince of Songkla University (REC 67-017-10-1).

In all cases, the diagnosis was established from imaging studies, tumor markers, intraoperative findings, and histopathologic findings. The primary tumor was examined with Computerized Tomography (CT scan), and the search for metastatic disease included chest CT, whole-body bone scan, and abdominal CT. Patients were staged with COG staging for extracranial germ cell tumors [2].

Depending on the staging, tumor site, and histopathology, patients were treated with either surgery alone or multimodal therapy with chemotherapy. All mature teratomas whose tumor was completely removed received no adjuvant chemotherapy. Cases with immature teratomas received chemotherapy according to their risk category. Chemotherapy in our institute followed the Thai Pediatric Oncology Group (TPOG) protocol (2016) [19]. Briefly, the therapy began with the combination of bleomycin, etoposide, and cisplatin (PEB regimen). In those who were not responsive to the PEB regimen, including progressive disease and relapse after completion of treatment, a combination of ifosfamide, carboplatin, and etoposide phosphate (ICE regimen) was used.

To analyze the postoperative change of AFP in non-benign cases, serial AFP values of the nearest time points from 1 week, one month, three months, six months, and one year were collected and analyzed. A non-benign case means a case in histological pathology other than benign GCT, which includes immature teratoma and all other malignant histology. Operative complications mean any complications occurring within 60 days after surgery.

Statistical analysis

Continuous data are presented as the mean and standard deviation for descriptive analysis. Categorical data are presented as percentages. Pre-operative AFP was categorized into ≤100 ng/ml, 100.1-50,000 ng/ml, and >50,000 ng/ml. Age at the diagnosis was grouped into those below 11 years old and those aged 11 years or more.

To offset very high levels of AFP in some cases, the post-operative change of AFP was analyzed on a log scale. The predictive correlation of log AFP levels at each time point was regressed against 5-year survival status and presented as receiver operating characteristic (ROC) curves, together with their corresponding area under the curve (AUC).

Survival outcomes were calculated as 5-year overall survival (OS) and 5-year recurrent free survival (RFS). The latter used recurrence, new metastases, death, or the latest follow-up for right censoring, whichever came first. Survival functions are displayed in the Kaplan-Meier curve fashion. Comparisons of survival probability used the Log-rank test. Univariable Cox's proportional hazard analysis was performed to estimate each significant variable's hazard ratio (HR). The receiver operating characteristic (ROC) curve was used to evaluate the prognostic performance of AFP in each time point against survival status in 5 years postoperation. HR was presented together with a 95% confidence interval (CI). All analyses were performed in Stata version 14.0 (Stata Corp.)The p-value of less than 0.05 was considered statistically significant. Construction of violin plots used Python 3.9 and its packages Pandas, Matplotlib, and Seaborn.

Results

Baseline characteristics

This study included 129 patients, 89 female (69%) and 40 male (31%). The age was divided into two groups: < 11 years and ≥ 11 years, which were 78 cases (60.5%) and 51 cases (39.5%), respectively. Regarding the histopathological subgroups, 46 cases (35.7%) were mature teratomas, 23 cases (17.8%) were immature teratomas, and 60 cases (46.5%) were malignant GCTs (Table 1). Considering tumor locations, 29 cases (22.5%) were sacrococcygeal tumors, 62 cases (48.1%) were gonadal tumors (ovary or testis), 19 cases (14.7%) were retroperitoneal tumors, 9 cases (7.0%) were mediastinal tumors, and 10 cases (7.8%) were other extragonadal tumors. Note that testicular tumors had the highest proportion of malignancy (66.7%). Initial AFP at the diagnosis was 0-100 ng/ml in 52 cases (42.6%), 100.1-50,000 ng/ml in 51 cases (41.8%), and > 50,000 ng/mL

in 19 cases (15.6%).

Operative complications occurred in 11 cases (8.5%), including intestinal ischemia in 3 cases, urinary leakage in 2 cases, and one case each of post-operative bleeding, renal vein injury, neurogenic bladder, renal failure, sepsis, and pleural effusion. Nine in eleven complications occurred to retroperitoneal tumors, 2 in vaginal tumors, and 1 in mediastinal GCT. There was 1 in-hospital mortality caused by an acute kidney injury during the postoperative period.

Survival outcomes and prognostic factors in all GCTs

The median follow-up period was 137 months. The 5-year OS of extracranial germ cell tumor patients in our institute was 87.4% (95% CI 79.2%- 92.5%), and the 5-year RFS was 82.6% (95% CI 73.7%- 88.7%) (Figure 1). The analysis found that clinicopathological factors significantly associated with poorer OS were male sex associated with poor survival sex, primary tumor site (retroperitoneal and extragonadal sites except for sacrococcygeal site), malignant histologic subgroup, initial AFP > 50,000 ng/mL, and presence of operative complications (Table 2). On analysis of RFS, significant factors predicting poorer RFS included male sex, malignant subgroup, and initial AFP > 50,000 ng/mL. On univariable Cox's proportional hazard analysis, endodermal sinus tumor/choriocarcinoma histology had the highest odds of failure in both OS and RFS, giving HR at 4.30 (95% CI 1.37-13.51) and 4.53 (95% CI 1.77-11.60), respectively. High initial AFP (> 100 mg/mL) had an HR in predicting poorer OS at 2.33 (95%CI 1.11-4.90) and RFS at 2.01 (95%CI 1.10-3.67). Operative complications were associated with poorer OS at the HR of 3.88, 95%CI 1.23-12.19. When multivariable Cox's proportional hazard analysis was performed, the presence of a surgical complication was the only factor independently associated with poorer OS (adjusted HR 4.56, 95%CI 1.29-16.13).

Subgroup analysis of non-benign GCTs

To perform a fine mapping for prognostic factors in moderate to high-risk eGCTs, those with benign diseases, which usually had excellent survival outcomes from the analysis. The subgroup then consisted of 23 cases of immature eGCTs and 60 cases of malignant eGCTs. On univariable survival analysis, the 5-year OS of the non-benign eGCTs was 84.8% (74.2%-91.3%), while the 5-year RFS was 78.1% (66.7%-86.8%). The survival outcomes of immature eGCTs were 100% when

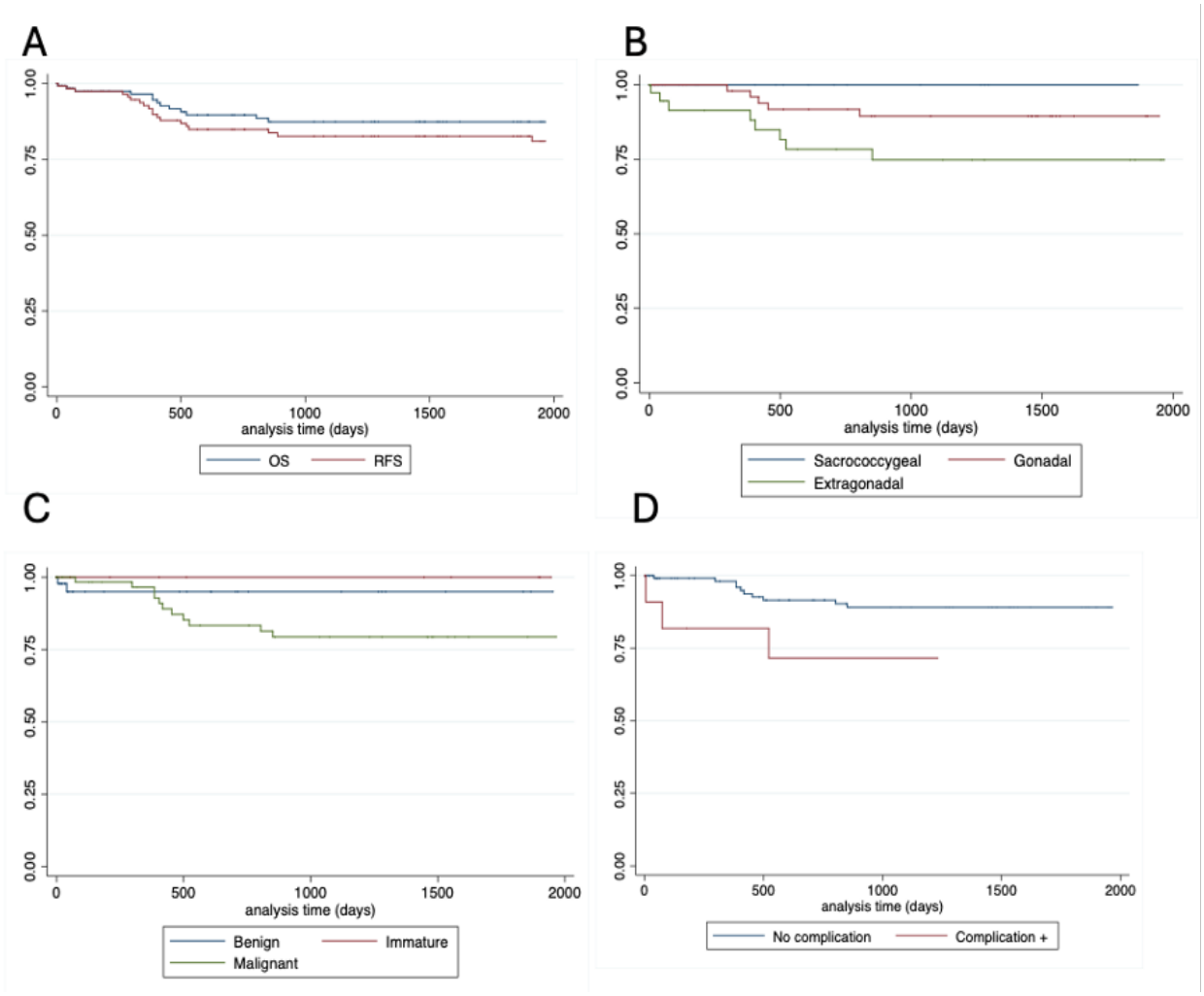

Figure 1. Kaplan-Meier Curves Showing Survival Outcomes of Germ Cell Tumors in This study. A) Overall survival (OS) and Recurrent-free survival (RFS), B) OS by primary tumor sites (log-rank p-value 0.012), C) RFS by histopathology groups (p-value 0.008), D) OS by the presence of sixty-day operative complications (p-value 0.008).

Table 1. Clinical Characteristics and Histological Types of Germ Cell Tumors in This Study (n: 129), According to the Primary Sites

Parameters	All N (%)	Ovary N (%)	Testis N (%)	Sacrococcygeal N (%)	Retroperitoneum N (%)	Others N (%)
Body weight (kg)*	25.9 (23.7)	43.2 (21.7)	7.7 (3.8)	7.0 (4.1)	9.3 (4.4)	25.7 (23.9)
Height (cm)*	110.1 (42.3)	145.3 (20.6)	83.5 (11.1)	67.9 (27.4)	78.7 (22.4)	110.5 (46.7)
Age						
< 1 year	38 (29.5)	0 (0.0)	0 (0.0)	18 (62.1)	12 (63.2)	8 (42.1)
1 to < 5 years	24 (18.6)	3 (5.4)	6 (100.0)	10 (34.5)	4 (21.1)	1 (5.26)
5 to < 10 years	12 (9.3)	7 (12.5)	0 (0.0)	1 (3.45)	2 (10.5)	2 (10.5)
10 to 15 years	55 (42.6)	46 (82.1)	0 (0.0)	0 (0.0)	1 (5.3)	8 (42.1)
Sex						
Female	89 (69.0)	56 (100.0)	0 (0.0)	16 (55.2)	8 (42.11)	9 (47.4)
Male	40 (31.0)	0 (0.0)	6 (100.0)	13 (44.8)	11 (57.9)	10 (52.6)
Histology						
Mature teratoma	46 (35.7)	13 (23.2)	2 (33.3)	19 (65.5)	7 (36.8)	5 (26.3)
Dysgerminoma	9 (7.0)	8 (14.2)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)
Immature teratoma	23 (17.8)	13 (23.2)	0 (0.0)	2 (6.9)	6 (31.6)	2 (10.5)
Malignant teratoma	3 (2.3)	1 (1.8)	0 (0.0)	1 (3.5)	1 (5.3)	0 (0.0)
Yolk sac tumor	46 (35.7)	20 (35.7) **	4 (66.7)	7 (24.1)	4 (21.0)	11 (57.8)
Choriocarcinoma	2 (1.5)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)
Malignant status						
Benign	46 (35.7)	13 (23.2)	2 (33.3)	19 (65.5)	7 (36.8)	5 (23.2)
Immature teratoma	23 (17.8)	13 (23.2)	0 (0.0)	2 (6.9)	6 (31.6)	2 (10.5)
Grade 1	10	6	-	-	4	-
Grade 2	5	2	-	1	1	1
Grade 3	8	5	-	1	1	1
Malignant	60 (46.5)	30 (53.6)	4 (66.7)	8 (27.6)	6 (31.6)	12 (63.2)
AFP***						
0-100 ng/mL	52 (42.6)	29 (55.8)	1 (20.0)	8 (28.6)	10 (52.6)	4 (22.2)
100.1-50,000 ng/mL	51 (41.8)	20 (38.4)	1 (20.0)	12 (42.9)	7 (36.8)	11 (61.1)
> 50,000 ng/mL	19 (15.6)	3 (5.8)	3 (60.0)	8 (28.6)	2 (10.5)	3 (16.7)

*, Presented as mean (standard deviation); **, One case of ovarian yolk sac tumor also had immature teratoma (grade 3) component;***AFP, Alphafetoprotein (data avalable in 122 cases)

the 5-year OS in malignant GCTs was 79.3% (95%CI 65.7%-88.0%) and the 5-year RFS was 70.3% (95%CI 56.0%-80.6%). On univariable survival analysis, factors significantly associated with worse survival outcomes included malignant status, and high initial AFP (> 100 mg/mL) (Table 3).

To focus on the sequential changes of post-operative AFP, serial AFP values are measured in sequence, from 1 week, one month, three months, six months, and one year. The median reduction of AFP value was 73.6 % after the first post-operative week, 85.8% in benign cases, 77.6% in the immature teratoma group, and 73.4% in malignant cases. On a log scale, there was no statistically significant difference in log-AFP value when comparing the immature and the malignant eGCTs during follow-up. However, when comparing those who survived until five post-operative years and those who did not, the log-AFP values of the two groups began to show a significant difference from 1 month (Figure 2). Cases with log AFP more than 2 (or absolute value > 100 ng/mL) were more likely to have events within five years. When the log-AFP value at each postoperative time point was plotted against the five-year survival status as a ROC curve, the AFP at one month and six months had the highest area under the ROC curve at 0.79 and 0.97, respectively (Figure 3, 4).

Discussion

Pediatric germ cell tumors are a group of embryonal tumors that arise from primordial germ cells (PGCs), specialized cells that migrate during embryogenesis to form the gonads (testes or ovaries) [1]. Any errors in this migration process, such as misplacement or incomplete migration, can lead to PGCs remaining in extragonadal sites. These misplaced PGCs may fail to differentiate properly and undergo abnormal proliferation and tumorigenesis [4, 20]. Regarding pathogenesis, pediatric germ cell neoplasms occur in various anatomical sites and present high heterogeneity. CT has two peaks of age incidences: young children < 4 years and adolescents

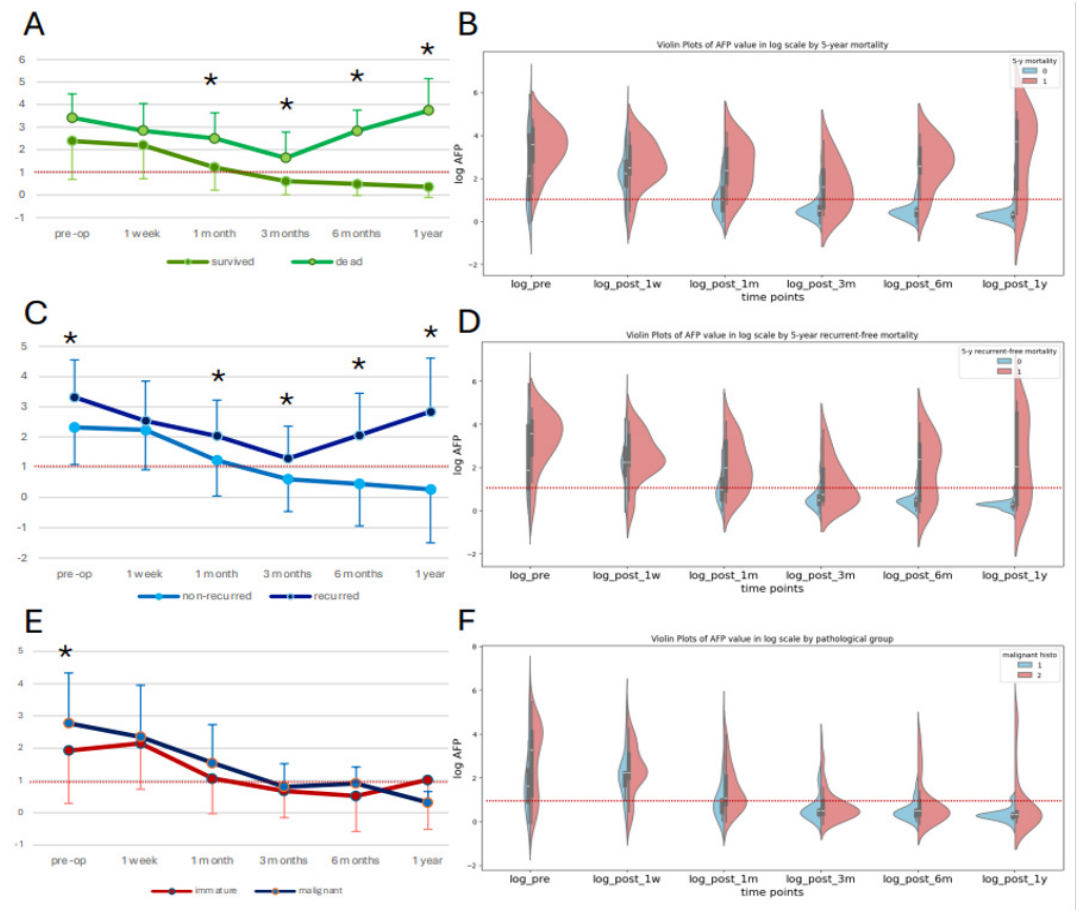

Figure 2. Time-Series of Alpha-Fetoprotein Level in Logarithmic Scale (log AFP) in Non-Benign Cases (n; 83). A, B: Comparing survived and mortality cases in a 5-year overall survival analysis. C, D: Comparing failure and non-failure cases in a 5-year recurrent-free survival analysis. E, F: Comparing between immature teratoma histology and malignant histology. A, C, and E showed mean values and standard deviation of log AFP at each time point. B, D, and F showed violin plots for each comparison. *: p-value < 0.05; horizontal red lines mark the value of 1.0 on the log scale, which is ten on the arithmetic scale.

(15-19 years) [21]. The most common eGCTs in young children in our study were sacrococcygeal teratoma, followed by retroperitoneal tumors and testicular tumors, while the majority of teenage sGCTs were ovarian tumors.

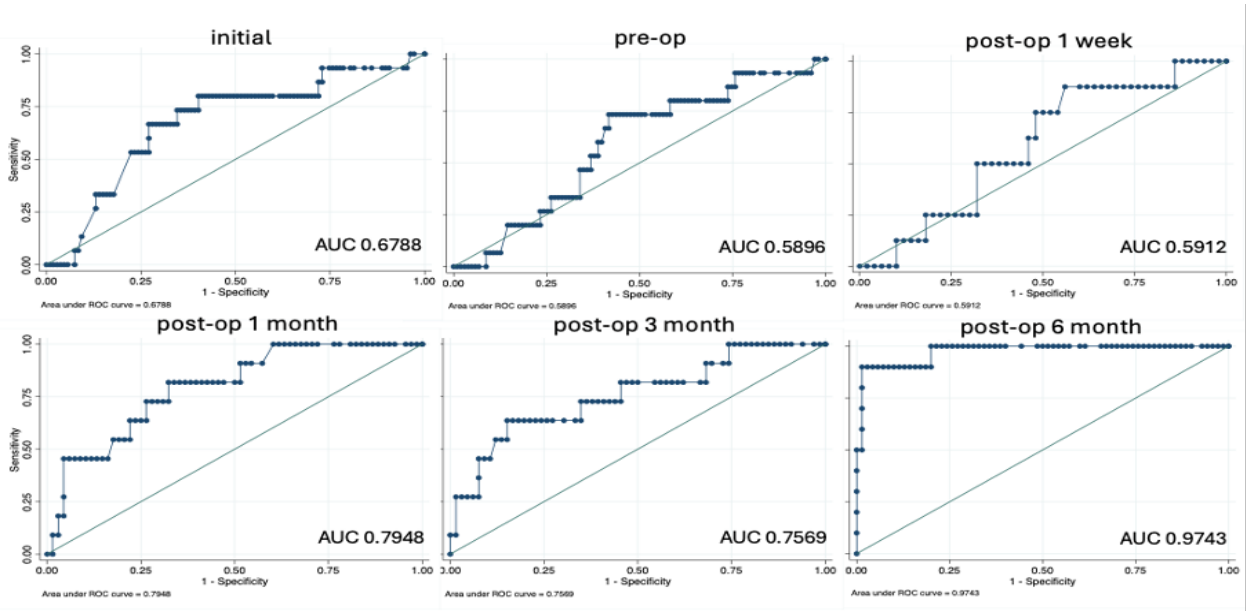

Figure 3. Receiver Operating Characteristic curves of log-APF Values in Multiple Time Points in Predicting Survival in a Five-Year Postoperative Period in Non-Benign GCTs.

Table 2. Association between Clinicopathological Parameters and Survival Outcomes in Germ Cell Tumors

	No (%)	5-year RFS (%)	p-value	5-year OS (%)	p-value
All	129 (100.0)	82.6 (73.7-88.7)	-	87.4 (79.2-92.5)	-
Sex					
Female	89 (69.0)	88.8 (78.8-94.3)	0.012	91.4 (81.4-96.0)	0.049
Male	40 (31.0)	68.0 (48.3-81.5)		78.4 (59.7-89.2)	
Age					
< 11 years	78 (60.5)	83.8 (71.9-91.0)	0.593	90.5 (79.8-95.7)	0.192
> 11 years	51 (39.5)	80.7 (65.1-89.8)		82.8 (67.2-91.4)	
Primary site					
Sacrococcygeal	29 (22.5)	84.6 (58.9-94.8)	0.54	100 (100.0)	0.012
Gonad (ovary or testis)	62 (48.1)	85.9 (72.7-93.0)		89.6 (76.7-95.5)	
Retroperitoneal and others	38 (29.5)	75.1 (56.2-87.8)		74.8 (55.7-86.6)	
Histology					
Mature teratoma	46 (35.7)	95.0 (81.2-98.7)	0.001	95.0 (81.2-98.7)	0.009
Immature/malignant teratoma/Dysgerminoma	35 (27.1)	96.4 (77.2-99.5)		100 (100.0)	
Yolk sac tumor/Choriocarcinoma	48 (37.2)	65.1 (48.9-77.3)		73.8 (57.6-84.6)	
Malignant status					
Benign/Immature	69 (53.5)	96.8 (87.9-99.2)	0.008	96.8 (87.8-99.0)	0.072
Malignant	60 (46.5)	70.3 (56.0-80.6)		79.3 (65.7-88.0)	
Initial AFP*					
0-100 ng/mL	52 (42.6)	94.8 (79.9-98.7)	0.063	98.1 (87.1-99.7)	0.049
100.1-50,000 ng/mL	51 (41.8)	77.4 (62.0-87.2)		83.9 (69.1-92.0)	
> 50,000 ng/mL	19 (15.6)	64.9 (37.8-82.6)		69.6 (41.3-86.2)	
Operative complication					
No	118 (91.5)	83.7 (74.4-89.9)	0.142	89.0 (80.5-94.0)	0.012
Yes	11 (8.5)	71.6 (35.0-89.9)		71.6 (35.0-89.9)	

*AFP, Alphafetoprotein (data available in 122 cases)

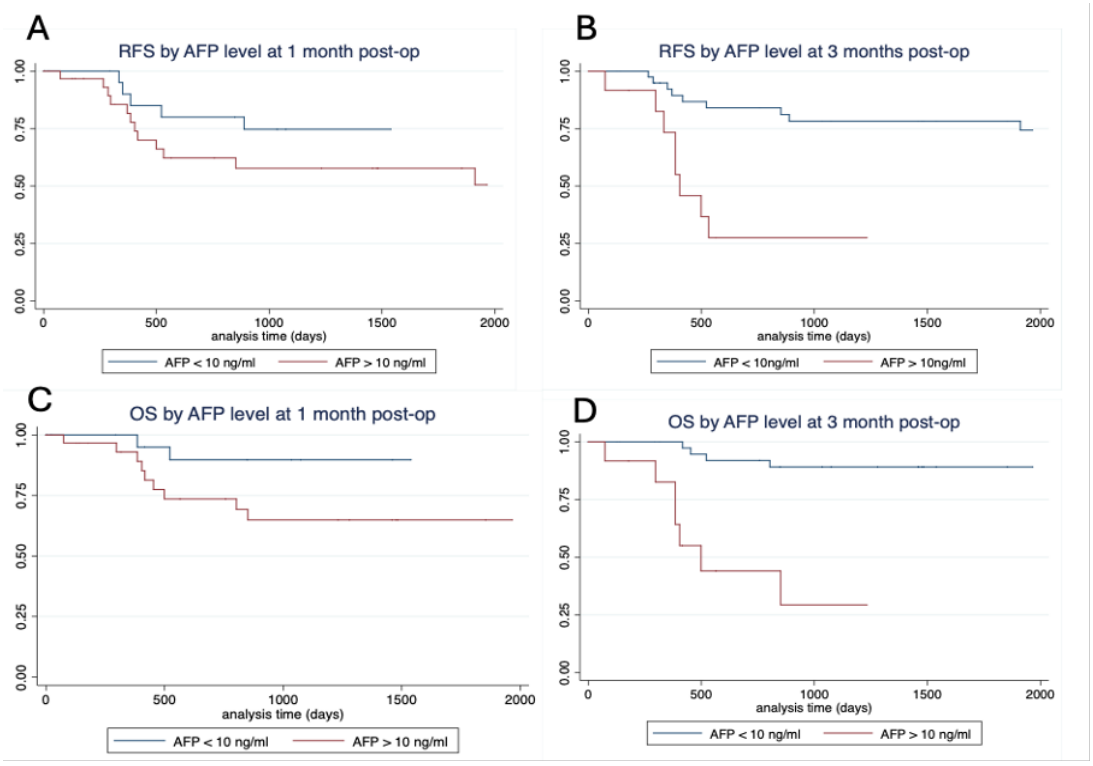

Figure 4. Kaplan-Meier Curves Showing Survival Outcomes of Non-Benign Germ Cell Tumors, According to Their Postoperative AFP Level at One and Three Months. A) Recurrent-free survival (RFS) by AFP at 1-month, B) RFS by AFP at 3-month, C) Overall survival (OS) by AFP at 1-month, B) OS by AFP at 3-month

Table 3. Survival Outcomes in Non-Benign Cases According to Malignant Features, Primary Sites and Chemotherapy

	No. (%)	5-year RFS (%)	p-value	5-year OS (%)	p-value
All non-benign cases	83 (100)	78.1 (66.7-86.0)		84.8 (74.2-91.3)	-
Malignant status					
Immature teratoma	23 (27.7)	100.0 (100.0)	0.006	100.0 (100.0)	0.036
Malignant histology	60 (72.3)	70.3 (56.0-80.6)		79.3 (65.7-88.0)	
Stage I/II	22	75.3 (50.3-88.9)	0.909	84.9 (60.1-94.9)	0.432
Stage III/IV	38	67.6 (49.0-80.6)		76.0 (57.6-87.2)	
Site					
Gonadal	36 (43.4)	69.5 (49.4-82.9)	0.331	79.9 (60.6-90.5)	0.344
Extragonadal	47 (56.6)	84.0 (69.2-92.0)		88.2 (73.8-94.9)	
Initial Alpha-fetoprotein					
0-100 ng/mL	26 (31.3)	95.2 (70.7-99.3)	0.016	100.0 (100.0)	0.004
100.1-50,000 ng/mL	42 (50.6)	75.8 (58.6-86.6)		83.7 (67.1-92.3)	
> 50,000 ng/mL	15 (18.1)	53.9 (24.3-76.3)		59.3 (27.3-81.1)	
Post-op Alpha-fetoprotein at 1 week					
> 50% of pre-op level	40 (67.8)	71.3 (60.2-87.3)	0.484	79.6 (60.0-90.3)	0.648
< 50% of pre-op level	19 (32.2)	79.4 (48.8-92.9)		86.7 (56.4-96.5)	
Post-op Alpha-fetoprotein at 1 month					
> 25% of pre-op level	50 (64.1)	76.9 (43.7-83.1)	0.587	86.6 (70.7-94.2)	0.132
< 25% of pre-op level	28 (35.9)	76.7 (43.7-83.1)		72.9 (49.3-86.8)	
Post-op Alpha-fetoprotein at 1 month					
< 10 ng/ml	40 (50.6)	83.8 (65.3-92.9)	0.031	93.4 (76.2-98.3)	0.017
> 10 ng/ml	39 (49.4)	63.1 (43.1-77.7)		69.4 (49.1-82.3)	
Post-op Alpha-fetoprotein at 3 month					
< 10 ng/ml	56 (72.7)	82.9 (68.7-91.1)	0.002	91.4 (78.8-96.7)	< 0.001
> 10 ng/ml	21 (27.3)	45.9 (20.2-68.4)		49.6 (21.3-72.7)	
Chemotherapy					
No	10 (12.0)	100.0 (100.0)	0.148	100.0 (100.0)	0.254
Yes	73 (88.0)	75.7 (63.4-84.4)		83.2 (71.6-90.3)	
PEB/JEB < 5 sessions	24				
PEB/JEB 5-6 sessions	35				
PEB/JEB > 6 sessions	14				

RFS, recurrent-free survival; OS, overall survival

Except for a case of benign sacrococcygeal GCT that later had a recurrence with a malignant yolk sac tumor, all cases of benign histology had excellent outcomes. Excluding benign cases, the reported OS of gonadal and extragonadal germ cell tumors have reached 91% and 81%, respectively [10]. Our survival of immature and malignant eGCT at 88% in the extragonadal site was comparable with previous reports when the figure of 80% in gonadal eGCT was relatively poorer, which might be explained by our higher incidence of therapeutic complications.

Our study did not find a difference in survival outcomes when comparing the adolescents and the younger age group. However, our study found correlations between OS and male sex, site (retroperitoneal and other extragonadal), histopathological type (yolk sac tumor/choriocarcinoma), and presence of operative complications. High initial AFP had a marginally significant association with OS at the p-value of 0.049. Our data that retroperitoneal eGCT was found in more proportion in males (27.5% of male eGCT compared to 9.0% in females) may explain the poorer survival rate in the male sex in our study. The association between sex and eGCT outcomes was inconsistent among previous reports [10, 22]. Previous studies also addressed poor prognosticating roles of the testicular site and completeness of surgical resection. However, our study could not demonstrate a poorer outcome in testicular GCT (5-year OS 80.0%). The presence of operative complications delayed the initiation of postoperative adjuvant chemotherapy. In addition, the complications itself may lead to the operative mortality. The surgical team must balance the extent of surgery and the risk of morbidity, especially in retroperitoneal teratoma.

AFP is a non-specific marker secreted by a yolk sac from the tenth week of pregnancy and by the fetal liver and digestive systems [2]. The protein has a 5-day half-life in the human body and usually has a physiologically high serum level in infants under eight months old [23, 24]. Non-benign germ cell tumors can produce AFP,

including yolk sac tumors, embryonal carcinomas, and immature teratomas. For these reasons, AFP was used as an adjunct for diagnosing germ cell tumors, assessing treatment response, and monitoring remission [2]. The prognosticating role of AFP in eGCT remains inconclusive. An analysis using COG's Malignant Germ Cell International Consortium data demonstrated that eGCTs with a satisfactory decline of AFP within the first two measures were less likely to have disease relapse [25]. A study from France focusing on malignant sacrococcygeal germ cell tumors emphasized a reduction of AFP within 3 months of surgery. It used a cut-off at 15,000 ng/ml as a part of risk stratification in their standard protocol (TGM95) [15]. However, the study found that AFP declines after the first chemotherapeutic course did not correlate with progress-free survival [26]. The aforementioned study speculated that a very high level of pre-treatment AFP might preclude a meaningful calculation of reduction after an intervention [26]. Our study evaluated the postoperative pattern of AFP using a logarithmic transformation and found that AFP in the first postoperative week might not significantly prognosticate the survival outcomes. However, log-AFP more than 2 (AFP > 100 ng/mL) after 1-3 months postoperative period was associated with worse survival outcomes. This evidence might be explained by the fact that, in the immediate postoperative period following removal of the gross pathology, serum AFP would reduce to some degree, regardless of the completeness of removal. Although the half-life of AFP is less than one week in theory, the first few postoperative weeks are also the ebb phase of tumor growth for the residual disease. After that phase, adjuvant chemotherapy was re-introduced, and the remaining cancer cells that resisted the drug regrew. At the same time, serum AFP in those cases with good response continued to decline at a quicker pace. The disparity of serum AFP between the good and poorer prognosis cases was even wider when the adjuvant therapy finished, from three months on. Although serum AFP in mortality cases varied, the value in survived cases was homogenously confined to less than 100 ng/mL along the follow-up course. The evidence suggested that intensive surveillance should be considered in cases whose AFP remains higher than this cut-off after three months.

The limitation of our study was that the number of cases was too small to perform a subgroup analysis for each individual pathological type or individual tumor site. However, the strength might be in the quality of follow-up data and the survival data from the population registry.

In conclusion, the study evaluated survival outcomes and factors associated with the outcomes of eGCTs in a center in Thailand. The study found that more than 84% of patients with eGCTs, 95% in benign cases, and 84.8% in non-benign cases, achieved long-term survival. Female sex, gonadal or sacrococcygeal sites, teratoma histology, initial AFP of less than 50,000 ng/mL, and uneventful surgery were associated with superior survival. Moreover, normalization of serum AFP at 1-3 months post-surgery prognosticated good outcomes.

Author Contribution Statement

Sasabong Tiyaamornwong: Principal investigator, Surgeon, Data collection, Data analysis, Manuscript draft. Polathep Vichitkunakorn: Give supervision to S.T in Data analysis. Pornpun Sripornsawan: Provide clinical data on clinical follow-up of the patients. Pongsakorn Choochuen: Data analysis. Chayut Pongpanit: Surgeon, Data collection. Kulpreeya sirichamratsakul: Surgeon, Data collection. Surasak Sangkhathat: Manuscript editing, Data analysis, Data visualization.

Acknowledgements

Funding

This research has received funding support from the National Science, Research and Innovation Fund (NSRF), and Prince of Songkla University, Thailand [grant number MED65051955].

Availability of data

The data presented in this manuscript can be provided by the author upon reasonable request

Ethics approval

The study was approved by the Human Research Ethics Committee of the Faculty of Medicine, Prince of Songkla University (HREC no. 67-017-10-1).

Conflict of interest

The authors declare no conflict of interest.

References

1. Pierce JL, Frazier AL, Amatruda JF. Pediatric germ cell tumors: A developmental perspective. Adv Urol. 2018;2018:9059382. https://doi.org/10.1155/2018/9059382.
2. Jezierska M, Gawrychowska A, Stefanowicz J. Diagnostic, prognostic and predictive markers in pediatric germ cell tumors-past, present and future. Diagnostics (Basel). 2022;12(2). https://doi.org/10.3390/diagnostics12020278.
3. Rescorla FJ. Germ cell tumors. Semin Pediatr Surg. 1997;6(1):29-37.
4. Zambrano E, Reyes-Múgica M. Pediatric germ cell tumors. Semin Diagn Pathol. 2023;40(1):52-62. https://doi.org/10.1053/j.semdp.2022.09.002.
5. Horton Z, Schlatter M, Schultz S. Pediatric germ cell tumors. Surg Oncol. 2007;16(3):205-13. https://doi.org/10.1016/j.suronc.2007.07.005.
6. Shaikh F, Murray MJ, Amatruda JF, Coleman N, Nicholson JC, Hale JP, et al. Paediatric extracranial germ-cell tumours. Lancet Oncol. 2016;17(4):e149-e62. https://doi.org/10.1016/s1470-2045(15)00545-8.
7. Agarwala S, Mitra A, Bansal D, Kapoor G, Vora T, Prasad M, et al. Management of pediatric malignant germ cell tumors: Icmr consensus document. Indian J Pediatr. 2017;84(6):465-72. https://doi.org/10.1007/s12098-017-2308-2.
8. Fergadis E, Gavrielatou N, Skouteris N, Athanasopoulos A, Lianos E, Kosmas C. Myeloablative chemotherapy and autologous stem cell transplantation can lead to successful postengraftment mobilization of hematopoietic progenitors to support planned subsequent cycle(s) of high-dose chemotherapy and autografting in a patient with relapsed germ-cell tumor. Anticancer Drugs. 2019;30(2):205-8.

https://doi.org/10.1097/cad.0000000000000714.
9. Ferhatoglu F, Paksoy N, Khanmammadov N, Yildiz A, Ahmed MA, Gülbas Z, et al. Therapeutic efficacy of high-dose chemotherapy with autologous stem-cell transplantation in 44 relapsed or refractory germ-cell tumor patients: A retrospective cohort study. Medicine (Baltimore). 2024;103(8):e37213. https://doi.org/10.1097/md.0000000000037213.
10. Hulsker CCC, El Mansori I, Fiocco M, Zsiros J, Wijnen MHW, Looijenga LHJ, et al. Treatment and survival of malignant extracranial germ cell tumours in the paediatric population: A systematic review and meta-analysis. Cancers (Basel). 2021;13(14). https://doi.org/10.3390/cancers13143561.
11. Ramanathan S, Prasad M, Vora T, Badira CP, Kembhavi S, Ramadwar M, et al. Outcomes of relapsed/refractory extracranial germ cell tumors treated on conventional salvage chemotherapy without stem cell rescue: Experience from a tertiary cancer center. Pediatr Blood Cancer. 2023;70(4):e30179. https://doi.org/10.1002/pbc.30179.
12. Baranzelli MC, Bouffet E, Quintana E, Portas M, Thyss A, Patte C. Non-seminomatous ovarian germ cell tumours in children. Eur J Cancer. 2000;36(3):376-83. https://doi.org/10.1016/s0959-8049(99)00317-2.
13. Frazier AL, Rumcheva P, Olson T, Giller R, Cushing B, Cullen J, et al. Application of the adult international germ cell classification system to pediatric malignant non-seminomatous germ cell tumors: A report from the children's oncology group. Pediatr Blood Cancer. 2008;50(4):746-51. https://doi.org/10.1002/pbc.21304.
14. Tangjitgamol S, Hanprasertpong J, Manusirivithaya S, Wootipoom V, Thavaramara T, Buhachat R. Malignant ovarian germ cell tumors: Clinico-pathological presentation and survival outcomes. Acta Obstet Gynecol Scand. 2010;89(2):182-9. https://doi.org/10.3109/00016340903443684.
15. De Corti F, Sarnacki S, Patte C, Mosseri V, Baranzelli MC, Martelli H, et al. Prognosis of malignant sacrococcygeal germ cell tumours according to their natural history and surgical management. Surg Oncol. 2012;21(2):e31-7. https://doi.org/10.1016/j.suronc.2012.03.001.
16. Frazier AL, Hale JP, Rodriguez-Galindo C, Dang H, Olson T, Murray MJ, et al. Revised risk classification for pediatric extracranial germ cell tumors based on 25 years of clinical trial data from the united kingdom and united states. J Clin Oncol. 2015;33(2):195-201. https://doi.org/10.1200/jco.2014.58.3369.
17. Calaminus G, Schneider DT, Bökkerink JP, Gadner H, Harms D, Willers R, et al. Prognostic value of tumor size, metastases, extension into bone, and increased tumor marker in children with malignant sacrococcygeal germ cell tumors: A prospective evaluation of 71 patients treated in the german cooperative protocols maligne keimzelltumoren (makei) 83/86 and makei 89. J Clin Oncol. 2003;21(5):781-6. https://doi.org/10.1200/jco.2003.03.125.
18. Marina N, London WB, Frazier AL, Lauer S, Rescorla F, Cushing B, et al. Prognostic factors in children with extragonadal malignant germ cell tumors: A pediatric intergroup study. J Clin Oncol. 2006;24(16):2544-8. https://doi.org/10.1200/jco.2005.04.1251.
19. The thai pediatric oncology group. National protocol for the treatment of childhood cancers 2016 [internet]. Thailand: The thai society of hematology; 2016 [cited 2016 jan]. Available from: Http://www.Thaipog.Net/news_detail.Php?I=d1fe173d08e959397adf34b1d77e88d7.
20. Müller MR, Skowron MA, Albers P, Nettersheim D. Molecular and epigenetic pathogenesis of germ cell tumors. Asian J Urol. 2021;8(2):144-54. https://doi.org/10.1016/j.ajur.2020.05.009.
21. Lew CZ, Liu HC, Hou JY, Huang TH, Yeh TC. Pediatric extracranial germ cell tumors: Review of clinics and perspectives in application of autologous stem cell transplantation. Cancers (Basel). 2023;15(7). https://doi.org/10.3390/cancers15071998.
22. Laohverapanich K, Buaboonnam J, Vathana N, Sanpakit K, Takpradit C, Narkbunnum N, et al. Clinical outcomes of extracranial germ cell tumors: A single institute's experience. Siriraj Med J. 2021;73(10):690-86. Https://doi.Org/10.33192/smj.2021.87.
23. Han SJ, Yoo S, Choi SH, Hwang EH. Actual half-life of alpha-fetoprotein as a prognostic tool in pediatric malignant tumors. Pediatr Surg Int. 1997;12(8):599-602. https://doi.org/10.1007/bf01371908.
24. Schneider DT, Calaminus G, Göbel U. Diagnostic value of alpha 1-fetoprotein and beta-human chorionic gonadotropin in infancy and childhood. Pediatr Hematol Oncol. 2001;18(1):11-26. https://doi.org/10.1080/088800101750059828.
25. O'Neill AF, Xia C, Krailo MD, Shaikh F, Pashankar FD, Billmire DF, et al. A-fetoprotein as a predictor of outcome for children with germ cell tumors: A report from the malignant germ cell international consortium. Cancer. 2019;125(20):3649-56. https://doi.org/10.1002/cncr.32363.
26. Fresneau B, Orbach D, Faure-Conter C, Sudour-Bonnange H, Vérité C, Gandemer V, et al. Is alpha-fetoprotein decline a prognostic factor of childhood non-seminomatous germ cell tumours? Results of the french tgm95 study. Eur J Cancer. 2018;95:11-9. https://doi.org/10.1016/j.ejca.2018.02.029.