

# Clinicopathological Evaluation of Extragonadal Germ Cell Tumors - A Retrospective Study from a Regional Cancer Center in India

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## Abstract

**Introduction:** Extragonadal germ cell tumors (EGGCTs) are tumors arising at extragonadal anatomical locations. The biological behavior and prognosis of these tumors differ from their gonadal counterparts. Our study aims to analyze their histological subtypes, the outcome, and the prognosis of these lesions at various age groups. **Material and Methods:** We carried out a retrospective analysis of all patients with EGGCTs diagnosed from January 2017 to December 2019. **Results:** Our study included 61 cases of EGGCTs. These cases were divided into neonatal (birth to six months), prepubertal (more than six months to 12 years), and post-pubertal group (>12 years). The most frequently affected group was prepubertal (44.2%). The age ranged from birth to 45 years with a male-to-female ratio of 1:1.03. The frequently involved site was sacrococcyx (36%) followed by mediastinum (31.1%). The common histologic subtype was mature teratoma (39.3%), followed by yolk sac tumor (YST) (18%), mixed germ cell tumor (18%), immature teratoma (14.7%), and germinoma (9.8%). Four cases of teratoma had somatic malignancies. There were 48 stage I, 8 stage II, and 2 stage III tumors. Statistical analysis revealed a significant association of age group concerning primary site ( $p=0.004$ ), histological type ( $p=0.002$ ), and clinical stage ( $p=0.034$ ). In a median follow-up of 30 months, an Overall Survival (OS) of 93.2% and Event Free Survival (EFS) of 90.4% were noted across all age groups. OS of 100% (neonatal), 96% (prepubertal) and 88.0% (post-pubertal) revealing a declining trend ( $p=0.324$ ) with increasing age was noted. The important prognostic factors include histological subtype (mixed germ cell tumors and teratomas with somatic malignancies had reduced overall survival) and stage (I vs II and III) for OS and stage alone for EFS ( $P<0.0001$ ). **Conclusion:** Our study highlights the clinicopathological characteristics, prognostic parameters, and the outcome of GCTs occurring at extragonadal sites and emphasizes the role of pathologists in the detailed reporting of these lesions.

**Keywords:** Extragonadal germ cell tumors- congenital- prepubertal- post-pubertal

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## Introduction

Extragonadal germ cell tumors (EGGCTs) are relatively uncommon, representing 1% to 5% of all germ cell tumors (GCTs) [1]. Predicting the behavior of these tumors differs significantly from their gonadal counterparts and depends on a combination of factors,

including age, anatomical site, histologic subtype, and clinical stage. In this study, we aim to investigate these biologically diverse and rare neoplasms while evaluating their important prognostic parameters.

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## Materials and Methods

We carried out a retrospective analysis of all cases of EGGCTs diagnosed by both biopsy and resection at our institute from January 2017 to December 2019. Patients with primary gonadal tumors presenting with metastasis to extragonadal location or with streak gonads with or without a history of gonadal germ cell tumors were excluded. Clinical presentation, serum tumor markers (alpha-fetoprotein (AFP),  $\beta$  human Chorionic Gonadotrophin ( $\beta$  hCG) and Lactate Dehydrogenase (LDH)), primary site, clinical staging, treatment, and follow-up information were collected from the medical records. Children's Oncology Group (COG) staging [2] for pediatric GCTs, Moran and Suster system staging [3] for adult mediastinal GCTs, and soft tissue sarcoma staging by American Joint Committee on Cancer (AJCC-8th edition) for adult retroperitoneal and sacrococcygeal GCTs were followed. All the histopathology slides were retrieved from filing and reviewed by two Onco-pathologists for histological subtype, margin status, coccyx involvement (in cases of sacrococcygeal teratoma), and treatment response (in those who received neoadjuvant chemotherapy (NACT)). The response was scored histologically according to International Germ Cell Consensus Classification Group (IGCCCG) criteria [4] with  $<10\%$  viable non-teratomatous tumor as a good response. The following immunohistochemical markers were used according to the histomorphology: SALL4, OCT 3/4, CD 117, Glypican 3, CD 30, AFP, and synaptophysin. Recurrence was defined by the re-emergence of serum Alpha-Fetoprotein (AFP) levels in a previously documented normal level or radiological evidence of tumor. Progressive disease refractory to treatment was defined as persistent increase in serum AFP/ increase in tumor size and/or distant metastasis.

The patients were categorized into three subcategories based on the College of American Pathologists (CAP) criteria: congenital/ neonatal (birth to 6 months), prepubertal (7 months to 11 years), and post-pubertal ( $\geq 12$  years). The data thus obtained were analyzed.

### Statistical Analysis

Statistical analysis was done using the software "R". Baseline parameters were analyzed using descriptive statistics. The association of the three subcategories to various parameters like the primary site, histological subtype, and clinical stage were analyzed using the Chi-square test and Fisher Exact test. P value  $<0.05$  was considered to be statistically significant. Overall Survival (OS) and Event Free Survival (EFS) were estimated using Kaplan-Meier analysis. Overall survival was defined as the time from study entry until death or last follow-up. Event-free survival is defined as the time from study entry till the first occurrence of disease progression, relapse, or until the last contact.

## Results

### Observation

Our study encompassed 61 cases of EGGCTs. The age range of affected individuals spanned from birth to 45 years with a median age of six years. Among the three defined age groups, the prepubertal group comprised the majority (44.2%), followed by post-pubertal (40.9%) and neonatal (14.7%). The post-pubertal group displayed a male preponderance (2.7:1) whereas the neonatal group exhibited a female preponderance (1:4). Sacrococcyx (22, 36%) was the most common site affected followed by the mediastinum (19, 21.3%), and retroperitoneum (13, 31.1%). Additionally, three cases of intracranial germ cell tumors were observed, with one each located in the thalamus, the third ventricle, and posterior falx. Uncommon sites of involvement included the vagina (2), rectum (1), and stomach (1). The clinical presentation of cases differed according to the site of presentation. Sacrococcygeal lesions typically presented with an external sacral mass (63.6%) or as a presacral mass without externalization (36.3%). Mediastinal tumors manifested with symptoms such as cough (26%), breathlessness (47%), and chest pain (38%). Retroperitoneal tumors presented with abdominal distension (36%) and abdominal pain (58%). Sacrococcyx was the common site involved in the congenital and prepubertal group while mediastinum was the most common site in the post-pubertal group ( $p=0.004$ ).

Table 1 displays the distribution of cases based on anatomical site and histological subtype within each subgroup.

### Histopathological diagnosis

a) Teratomas: Teratomas were the most common histological type across all age groups (54%). This category included 24 cases of mature and nine cases of immature teratomas. The sacrococcyx was the most common site (39.3%) followed by the retroperitoneum and mediastinum comprising 27.2% each. Two cases of teratoma were noted in the gastrointestinal tract, one in the stomach (Figure 1) and one in the rectum.

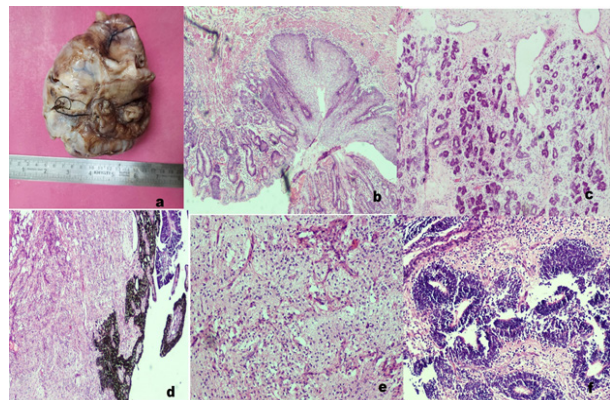


Figure 1. Gastric teratoma a) Gross image b) Gastroesophageal junction c) adnexal glands, d) retinal pigment epithelium, e) glial tissue f) immature neuroepithelium (H&E, 40x)

Table 1. Distribution of Extragonadal Germ Cell Tumors at Various Locations in Each Group and Its Histological subtypes

	Congenital/ Neonatal	Prepubertal	Postpubertal	Total (%)	P value
Total No. of Cases	9 (14.7%)	27 (44.2%)	25 (40.9%)	61	
M: F	1:04	1.5:1.7	2.7:1	01:01.0	
Sites:					
Sacrococcygeal	6	13	3	22 (36)	
Retroperitoneum	2	6	5	13 (21.3)	
Mediastinum	1	4	14	19 (31.1)	0.004
Intracranial	-	-	3	3 (4.9)	
Other Sites	-	4	-	4(6.7)	
Histological Subtype:					
Mature Teratoma	6	12	6	24 (39.3)	
Immature Teratoma	3	3	3	9 (14.7)	
Yolk Sac Tumor (YST)	-	7	4	11 (18)	
Germinoma	-	-	6	6 (9.8)	0.002
Mixed Germ Cell Tumor (Teratoma+Yst)	-	3	6	11 (18)	
(Teratoma+Yst+Ec)	-	2	-	2 (3.3)	
Stage:					
I	9	25	14	48 (82.8)	
II	0	1	7	8 (13.80)	0.034
III	0	1	1	2 (3.4)	

Immature teratomas were graded according to the criteria followed for ovarian teratomas as grade I (4), grade II (2), and grade III tumors (3). In the neonatal group, all cases were diagnosed as teratomas (100%). Four cases of mature teratomas were associated with somatic malignancies, including three with colonic-type adenocarcinoma and one with both carcinoma and sarcoma (squamous cell carcinoma, chondrosarcoma, and neuroendocrine tumor) (Figure 2). In one case of a mediastinal lesion, a definitive diagnosis of teratoma could not be made despite repeated biopsies due to scanty or not representative tissue. The final diagnosis was established upon resected specimen examination as mature teratoma with adenocarcinoma. Another case of mediastinal teratoma with adenocarcinoma was diagnosed as primary adenocarcinoma, possibly of thymic origin, on biopsy.

b) Germinomas: This histological subtype of GCT was seen exclusively in the post-pubertal group (100%). The most common site was the mediastinum (50%) followed by intracranium (33.3%) and retroperitoneum (16.6%). Elevated serum  $\beta$ -hCG was observed in 50% of cases. All the cases exhibited classic histomorphology of germinoma on biopsy and the same was confirmed by immunomarkers.

c) Yolk sac tumor (YST): Out of 11 cases of YST, 7 cases (63%) were noted in the prepubertal age group. The sacrococcyx was the most common site involved (55.5%) followed by the retroperitoneum (18.1%), mediastinum (9.09%), vagina (18.1%), and intracranium (9.09%). All the cases displayed elevated serum AFP levels ranging from 250 U/L to >50,000 U/L and were diagnosed via biopsy, confirmed by SALL4 and Glypican

3 im-munohistochemistry.

d) Mixed germ cell tumor (MGCT): Our study included 11 cases of mixed germ cell tumors. The most common site was the mediastinum (54.5%) followed by the sacrococcyx (36.3%) and the retroperitoneum (9.09%). MGCT was observed only in the post-pubertal (54.5%) and prepubertal (45.4%) groups. The mixed germ cell tumor components comprised teratoma with YST (9 cases), teratoma with YST, and embryonal carcinoma (EC) (2 cases).

No other associated malignancies or syndromes were observed in our study.

#### Staging, treatment, follow-up, and outcome:

Our study included 48 stage I, eight stage II, and two stage III EGGCT tumors. Intracranial tumors were not staged. All cases of teratomas (both mature and immature) underwent upfront resection while all cases of malignant germ cell tumors received NACT with six cycles of JEB (Carboplatin, Etoposide, and Bleomycin) in patients < 2 years of age and four cycles of BEP (Bleomycin, Etoposide, and Cisplatin) in patients >2 years. Resection of the residual mass was done following NACT. Recurrent and refractory cases to first-line treatment received salvage chemotherapy with two cycles of TIC (Etoposide, Ifosfamide, and Carboplatin). Our follow-up period ranged from 4 months to 68 months with a median follow-up duration of 30 months.

Neonatal group: This group included nine cases (14.7%). All the cases were exclusively teratomas and were categorized as COG stage I. These cases underwent upfront surgery with complete tumor excision.



Table 2. List of 9 Cases with Recurrent, Refractory, or Metastatic Disease

Case No.	Age in Years / Sex	Location	HPE Diagnosis	Clinical Stage	Treatment	Outcome	Probable Reason
1	1/M	Sacrococcygeal	Immature teratoma	II	Upfront surgery	*RC -10m (IT+YST)	Positive margin, Inadequate sampling
2	8/M	Sacrococcygeal	Mixed GCT (Mature teratoma + YST)	I	NACT+surgery	*RC-1 y MGCT (MT+ YST)	---
3	3.5/F	Vagina	YST	III (inguinal LN +)	NACT+ surgery+	*RC -6 m (YST)	Incomplete response
4	2/F	Vagina	YST	I	NACT+ Surgery+	*RC -8 m (YST)	Incomplete response
5	4/M	Retroperitoneum	Mixed GCT (Immature teratoma+YST)	I	Salvage CT followed by surgery	Lung metastasis and D- 1y	Refractory to treatment, disease progression
6	20/F	Retroperitoneum	Immature teratoma	II	Upfront surgery	*RC- 2y (YST)	Positive margin, Inadequate sampling
7	28/M	Mediastinum	MT with SM	III (lung)	Upfront surgery	**D-4m	Higher CS
8	36/M	Mediastinum	MT with SM	II (Pleura +)	Upfront surgery	**D-7m	Higher CS
9	35/M	Mediastinum	MT	II (Pleura +)	Upfront surgery	**D-6m	Higher CS

\*RC- Recurrence, \*\*D- Death IT- Immature teratoma, MT- Mature Teratoma, LN- Lymph nodes, SM- somatic malignancy, CS- clinical stage, CT- Chemotherapy, m- months, y- years (Cases-1 to5- COG staging, Cases 7-9- Moran and suster staging, Case 6-AJCC soft tissue sarcoma staging)

Coccygectomy was performed in all sacrococcygeal teratomas and coccyx involvement was noted in two out of six cases. None of the neonatal cases displayed recurrence or distant me-tastasis during the follow-up period.

Table 2 provides a list of cases with recurrent, refractory, or metastatic disease.

Prepubertal group: The majority (44.2%) of our cases belonged to this group. The incidence of YST was higher in this age group when compared to other groups (63.6%). The stage distribution was as follows: 92.6% of cases were in stage I and 7.4% of cases were in II - III. A single case of retroperitoneal mixed GCT was refractory to treatment, developed lung metastasis, and succumbed despite salvage chemotherapy (Case 5). Two cases of YST, one case of mixed germ cell tumor (immature teratoma +YST), and one immature teratoma developed recurrence 6, 8, 12, and 10 months later, respectively (Case 3, 4, 5, and 1). All four cases received salvage chemotherapy and achieved complete remission.

#### Post-pubertal group

In our study, 40.9% of cases were post-pubertal adults. Teratomas were the common tumors, followed by germinomas and MGCT, comprising 24% each. The mediastinal tu-mors were staged according to Moran and Suster staging as stage I (78.5%), stage II (14.2%), and stage III (7.1%). Retroperitoneal and sacrococcygeal tumors were staged according to the AJCC soft tissue sarcoma staging system as stage I (37.5%) and stage II (62.5%). All cases of teratomas underwent upfront complete resection and had an uneventful follow-up, except a single case of ret-roperitoneal immature teratoma that recurred as a yolk sac tumor two years later (case 6). All cases of MGCT exhibited a good histological response to NACT and achieved complete remission. 14.2% of cases in this group were associated with somatic malignancies. The mortality rate was higher in this group (12%) and all cases occurred in mediastinal location and presented at stages II and III.

The present study revealed a statistically significant correlation between histological type and stage

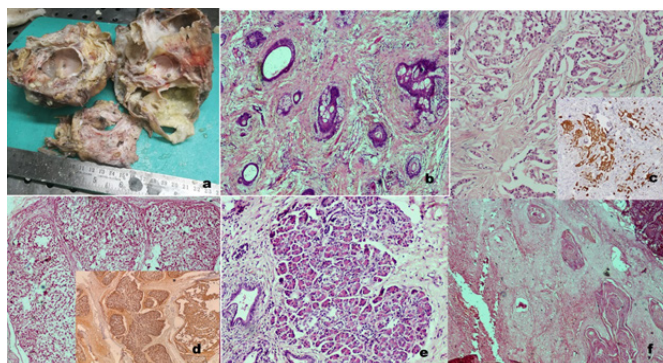


Figure 2. Retroperitoneal Teratoma in a 3-year-old boy (a) Gross Image Showing Tumor with Solid Cystic Areas and Component of Bone b) Microscopy: skin adnexal structures c) Carcinoid tumor showing cells in nests and cords (inset- IHC- synaptophysin positive in neoplastic cells) d) Chondrosarcoma (inset – S100 positive), e) Pancreatic tissue, f) Squamous cell carcinoma. (H&E, 40x)

Table 3. Overall Survival and Event-free Survival Analysis of EGGCTs

Parameters	Estimated OS (%)	P value	Estimated EFS (%)	P value
Overall	93.40		90.20	
Categories				
· Neonatal	100.00		100.00	
· Prepubertal	96.30	0.324	81.50	0.129
· Post-pubertal	88.00		96.00	
Tumor site				
· Sacrococcyx	100.00		90.90	
· Retroperitoneum	92.30	0.239	84.60	0.446
· Mediastinum	84.20		100.00	
· Intracranium	100.00		100.00	
Clinical stage				
· I	97.90		93.80	
· II	75	<0.001	75	<0.001
· III	50		50	

concerning age. In the neonatal group, all cases were exclusively teratomas. In the prepubertal group, only non-seminomatous tumors were observed, whereas in the post-pubertal group, both seminomatous and non-seminomatous tumors were noted ( $p=0.002$ ). In the neonatal group, all tumors presented in stage I in contrast to the prepubertal (92.6%) and post-pubertal group (78.5%) ( $p=0.034$ ). The estimated O.S was 93.4% and EFS was 90.2% across all age groups. Overall survival of 100% was observed in the neonatal, 96.3% in the prepubertal and 88.0% in the post-pubertal group showing a declining trend with increasing age ( $p=0.324$ ), although not statistically significant (Figure 3). An excellent prognosis was noted in the neonatal group regardless of the tumor location. The prepubertal group showed a higher percentage of recurrence with the least EFS (81.8%) among the three subgroups. We observed poorer OS in mediastinal lesions (84.2%) ( $p=0.239$ ) and the least EFS in retroperitoneal lesions (84.6%) ( $p=0.446$ ). Kaplan-Meier analysis identified histological subtype as a significant prognostic parameter with  $p<0.001$  in OS

analysis. Mixed germ cell tumors and teratomas with somatic malignancies displayed decreased OS (90.9% and 20% respectively) compared to other tumors (100%). A higher recurrence rate was observed in pure yolk sac tumors, with the least EFS of 81.8% ( $p=0.762$ ). Stage was a significant parameter in OS and EFS analysis, with stage III tumors exhibiting the lowest survival (50% OS and EFS) ( $p<0.001$ ).

Table 3 provides the survival analysis of EGGCTs concerning age, tumor site, histological subtype, and clinical stage.

## Discussion

EGGCTs arise from the aberrant lodging of primordial germ cells along the midline during their migration [5]. Histologically, EGGCTs exhibit similarities to gonadal germ cell tumors but they differ in their clinical and biological behavior. Shared features with gonadal germ cell tumors include their common occurrence in young individuals, elevated serum markers, responsiveness to

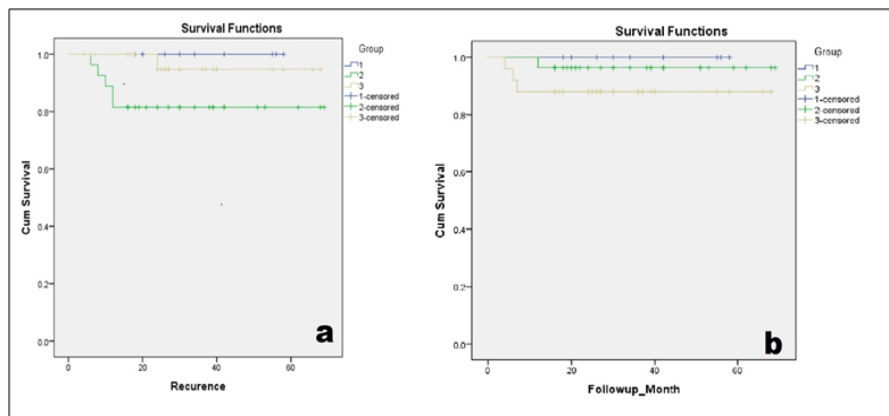


Figure 3. Overall Survival and Disease-free Survival Analysis in Three Subgroups of Cases. a. Event-free survival (EFS), ( $p$ -value= 0.129) b. Overall survival (OS) in months ( $p$  value=0.324). Group: 1- neonatal, Group 2- prepubertal, Group 3- post-pubertal

cisplatin-based chemotherapy, and the presence of i (12p) abnormality. However, several distinctive features set EGGCTs apart, including their frequent presentations with larger tumor masses, varying prognoses associated with age, tumor location, a predominance of non-seminomatous components, and unique associations with Klinefelter syndrome and hematological neoplasms that often prove refractory to treatment [6].

#### *Congenital/Neonatal Group*

In this group, all cases in our study were teratomas. The most prevalent site was the sacrococcyx where we observed a female predominance, aligning with existing literature [4, 5]. Other uncommon sites include the mediastinum, head and neck, and the retroperitoneum [6-11]. Although Issac et al. [12] have reported a 5% frequency of yolk sac tumors in congenital teratomas, we did not encounter any malignant GCTs in this age group. Furthermore, no recurrences or metastases were observed during the follow-up period, resulting in an OS and EFS of 100%. Our results were consistent with Mc. Kenney et al. [9], who observed no recurrences following the complete surgical removal of teratomas during a median follow-up of 36 months.

#### *Childhood (Prepubertal)*

In this group, we exclusively observed non-seminomatous germ cell tumors, with YSTs being the most prevalent subtype (69.2%), consistent with the findings of Schneider et al. [13]. Among the 27 prepubertal EGGCTs, four exhibited recurrences, including two yolk sac tumors, one immature teratoma, and one mixed germ cell tumor. Notable, one case of sacrococcygeal immature teratoma with a positive margin developed mixed GCT (YST+teratoma) 10 months post-surgery (case 1). Marina et al. [14] have identified foci of yolk sac tumors in 23 out of 73 cases of immature teratoma upon review, underscoring the need for extensive sampling and margin assessment in all cases of teratomas. This is crucial as some studies have reported the absence of a yolk sac in the primary tumor with the recurrence showing a yolk sac component. [15,16] Two of our cases of vaginal yolk sac tumor showed recurrences 6 months (case 3) and 8 months (case 4) later with an increase in serum AFP levels. Both the cases showed incomplete response to NACT with >50% viable tumor. Consequently, the assessment of viable non-teratomatous components becomes pivotal as it significantly influences prognosis. [17]

Mediastinal tumors in this group predominantly presented as teratomas or YSTs. Among our four mediastinal tumors, three were teratomas and one was a mixed germ cell tumor (teratoma and YST). The prognosis of mediastinal GCTs is closely linked to the extent of surgical excision [18]. In our study, all mediastinal GCTs were at stage I with negative margins, and their follow-up was uneventful. However, Kim et al. [19] showed poorer EFS in patients with mediastinal disease (n=12, 66.7%±13.6%) compared to those with non-mediastinal disease (n=54, 96.0%±2.8%) (p =0.001).

Retroperitoneal GCTs are very rare comprising

<5% of all EGGCTs [1]. We had six cases of retroperitoneal GCTs which included one case of mixed GCT (teratoma and YST) and five cases of teratoma. One of our cases of mature teratoma was associated with multiple somatic malignancies including squamous cell carcinoma, chondrosarcoma, and neuroendocrine tumor at presentation. Very few case reports have shown the simultaneous occurrence of carcinoma and sarcoma. Sarcomas more typically follows chemotherapy or late relapse [20]. Oosterhuis et al. [21] have reported a case of intestinal-type adenocarcinoma and a low-grade leiomyosarcoma in a late recurrence 19 years after the initial diagnosis of testicular GCT [21].

#### *Adults (Post-pubertal)*

In this age group, the mediastinum emerged as the commonly involved site (56%) with a male pre-dominance (male: female ratio of 2.7:1), a stark contrast to the other two subgroups. A study by Moran and Suster [3] found that out of 322 cases of mediastinal GCTs, 320 were noted in males. Unlike in other EGGCTs, the grading of immature teratomas and clinical staging, particularly in mediastinal lesions assumes greater prognostic significance [1]. In our study, two cases presented at stage II with pleural infiltration, and one at stage III with lung metastasis. All mediastinal teratomas in our study were mature teratomas, with three cases associated with somatic malignancies, all of which were adenocarcinomas. Fan J et al. [22] also observed that 90% of somatic malignancies arising from teratomas were adenocarcinomas. Two of our cases with somatic malignancies succumbed within seven and six months post-surgery respectively (Case 7 and 8) indicating the aggressive nature of this disease. A study on male EGGCTs by Busch et al. [23] showed that the 5-year overall survival in adult EGGCTs ranged from 40% to 90% and is more favorable for retroperitoneal seminomatous tumors than mediastinal non-seminomatous tumors.

In Conclusion, germ cell tumors must be considered in the differential diagnosis, as they can manifest across all age groups at various extragonadal locations. Age, histological subtype, and stage remain pivotal prognostic parameters in our study. Pathologists play a crucial role not only in clinching the correct diagnosis but also in evaluating the various prognostic factors that contribute to assessing the disease's outcome.

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