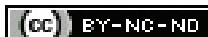


# Histomorphological Spectrum of Gonadal and Extragonadal Germ Cell Tumours at a Tertiary Cancer Centre in Southern Rajasthan, India

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## ABSTRACT

**Introduction:** Germ Cell Tumours (GCT) are heterogenous tumours believed to arise from primordial germ cells. The GCT predominantly affects gonads (testis and ovary) and also involves extragonadal sites, characteristically locations along midline of the body. The GCT of testis, ovary and extragonadal sites show peculiar histomorphological features and types subject to the age and site of patient. Definite histopathological typing of GCT is of vital importance to decide the further treatment. Till now, very few studies have been conducted in India on GCT of gonads and extragonadal sites.

**Aim:** To study the pathologic findings of GCT including macroscopic and microscopic features and to classify the tumours according to latest World Health Organisation (WHO) classification of GCT for designated site of origin.

**Materials and Methods:** Retrospective analysis was conducted including 141 cases of GCT of all sites, diagnosed at a tertiary cancer centre in Udaipur, Rajasthan, India between January 2016 to April 2021. Data were collected regarding demographic, clinical, gross and histopathological details. Results were analysed using Statistical Package of Social Sciences (SPSS) software Version 21.0. method.

**Results:** Germinal cell tumours shows various age ranges for different site of origin. Ovarian GCT age varies from seven years to 65 years. Age group of testicular GCT varies from 1-55 years. Extragonadal GCT (EG GCT) was seen as early as in four-day-old newborn. Out of 141 cases, 103 were ovarian, 21 were testicular and 17 were EG GCT cases. Most common ovarian GCT is Mature Teratoma (MT) (85 cases, 82.53%) and most common malignant ovarian GCT is dysgerminoma (9 cases, 8.74%). Most common testicular GCT type is Malignant Mixed GCT (MM GCT) (9 cases, 42.86%) followed by seminoma (5 cases, 23.81%) and Yolk Sac Tumours (YST) (3 cases, 14.29%). EG GCT involves retroperitoneum (5 cases, 29.41%), anterior mediastinum (4 cases, 23.53%), Sacrococcyx (3 cases, 17.65%) and Central Nervous System (CNS) (2 cases, 11.76%) with most common EG GCT is teratoma (9 cases, 52.94%)

**Conclusion:** Gonadal and extragonadal GCT share many common tumours, albeit, distinctive site-specific histopathological findings also present. These features often complicate the definitive diagnosis of GCT for pathologists, specifically in cases of MM GCT.

**Keywords:** Dysgerminoma, Gonadoblastoma, Mature and immature teratoma, Mediastinum, Seminoma, Yolk sac tumour

## INTRODUCTION

The GCT are a complex group of tumours arising due to abnormal differentiation of primordial germ cells showing striking heterogeneity regarding histomorphology and site of presentation [1,2]. The GCT commonly involves testis and ovary, although its prevalence is different at each of these organs [3]. The GCT involving extragonadal sites are rare and they constitute only 2-5% of malignant GCT. The EG GCT may involve sites along the midline of body from pineal gland in brain to the coccyx bone including mediastinum and retroperitoneum [4].

The GCT can affect patients of any age, albeit children and young adults are commonly affected [3]. Ovarian GCT account for 25-25% of all ovarian neoplasms. A 95% ovarian GCT is benign mature cystic teratoma, whereas only 5% of ovarian GCT is malignant in nature [5]. Testicular GCT is divided into seminoma and Non Seminomatous GCT (NSGCT), each make up about 50% of all testicular GCT [6]. Mediastinum is the most common site for EG GCT, accounting for about 50-70% of all EG GCT. The MTs account for 70-75% of all mediastinal GCT, whereas remaining 25-30% in mediastinum are malignant GCT [7].

Dysgerminoma is the most common malignant ovarian GCT, others being Immature Teratoma (IT), YST, Embryonal Carcinoma (EC), Non gestational choriocarcinoma and MM GCT [8]. Among testicular GCT, seminoma is the most common tumour, followed by EC, YST postpubertal type, trophoblastic tumours and teratoma postpubertal type. Mixed GCT accounts for about 70% of all

NSGCT. The GCT unrelated to Germ Cell Neoplasia In Situ (GCNIS) includes spermatocytic tumour, teratoma prepubertal type and YST prepubertal type [9]. Surgery plays an important role in treatment of GCT. Chemotherapy is applied in malignant GCT and Radiotherapy is recommended in case of radiosensitive seminoma [10]. The aim of the present study was to determine the proportion of various subtypes of GCT according to latest WHO classification [8,9]. Novelty of the study is specified by the fact that, very few articles have been published in literature incorporating GCT of all human body sites [3,4,7,10].

## MATERIALS AND METHODS

The present retrospective study was conducted at Geetanjali Medical College and Hospital, Udaipur, Rajasthan, India, data was collected in May 2021. Study included 141 cases who were diagnosed as GCT and treated between January 2016 to April 2021. All patients were diagnosed on Haematoxylin and Eosin (H&E) stained sections.

**Inclusion criteria:** Cases of testis, ovary and extragonadal tumours diagnosed as GCT and operated were included in the study.

**Exclusion criteria:** Cases without histopathological confirmation of gonadal or extragonadal mass or review cases from outside were excluded from the study.

All the cases were retrospectively analysed for their clinical presentation and pathological features. Key clinical parameters including gender, age, location of tumour were also noted. Pathological details include gross findings, laterality or any other significant features. Testis, Ovary

and Extragenadal GCT were graded benign or malignant according to standard guidelines of WHO classification book of respective system. Histopathological features including further subtyping were reported commensurate with the WHO classification of GCTs of Female Genital Tract 4<sup>th</sup> Edition (2014) [8] and WHO classification of GCTs of Male Genital Organs 4<sup>th</sup> Edition (2016) [9].

Sections were stained with H&E using Harris haematoxylin along with regressive staining method. After dewaxing procedure, rehydrate sections through graded alcohol. Stain in haematoxylin followed by bluing, differentiation and eosin stain. Dehydrate the sections through alcohol followed by clearing and mounting.

## STATISTICAL ANALYSIS

Data was entered in Microsoft Excel and statistical analysis was done using SPSS software Version 21.0. Frequency distribution was done for categorical variables and determined as proportions.

## RESULTS

Total 141 cases of gonadal GCT and EG GCT were studied including clinical and histological features [Table/Fig-1,2].

Variable	Testicular GCT	Ovarian GCT	EG GCT	Total
No. of cases	21	103	17	141
Age range (Years)	01 to 55	07 to 65	4 days to 55 years	-
Mean age (Years)	24	26	18	
Location				
Right	12 (57.14%)	64 (62.14%)		76 (53.90 %)
Left	09 (42.86%)	33 (32.04 %)	-	42 (29.79 %)
Bilateral	-	06 (5.82 %)		06 (4.25 %)
Nature				
Benign	02 (9.52%)	85 (82.52 %)	09 (52.94 %)	96 (68.09%)
Malignant	19 (90.48%)	18 (17.48 %)	08 (47.06 %)	45 (31.91 %)

[Table/Fig-1]: Clinical presentation of 141 cases of GCT.

Histology	Testicular GCTs (21)	Ovarian GCTs (103)	Extragenadal GCTs (17)	Total (141)
Mature teratoma	2 (9.52%)	85 (82.53%)	9 (52.94 %)	96 (68.08%)
Immature teratoma	-	1 (0.97%)	-	1 (0.71%)
Dysgerminoma	-	9 (8.74%)	-	9 (6.38%)
Seminoma	5 (23.81%)	-	3 (17.65%)	8 (5.67%)
Yolk sac tumour	3 (14.29%)	3 (2.91%)	-	6 (4.26%)
Embryonal carcinoma	2 (9.52%)	-	-	2 (1.42%)
Non gestational choriocarcinoma	-	2 (1.94%)	1 (5.88%)	3 (2.13%)
Mixed GCT	9 (42.86%)	3 (2.91%)	-	12 (8.51%)
GCT, NOS	-	-	4 (23.53 %)	4 (2.84%)

[Table/Fig-2]: Histopathological diagnosis of Germ Cell Tumours (GCTs).

GCT, NOS: Germ cell tumour, Not otherwise specified; EG GCT: Extra-gonadal germ cell tumour

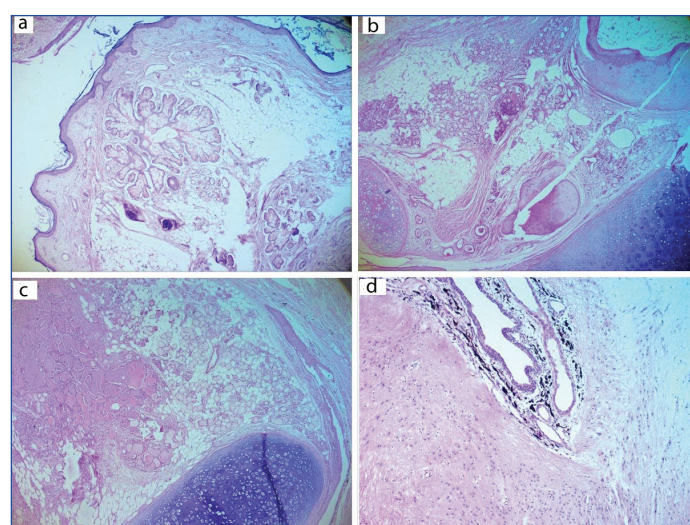
**Ovarian GCT:** The age group varies from seven to 65 years with mean age of 26 years. Out of total 103 cases, bilateral cases were six, whereas unilateral cases include 64 cases of right ovary and 33 cases of left ovary. Ninety-six patients presented with pain in abdomen with abdominal mass. Remaining seven patients presented with non specific symptoms. On gross examination, capsule was intact in 101 patients and was ruptured in one each case of microscopically confirmed YST and choriocarcinoma. On microscopy, MT was the predominant tumour (85 cases, 82.52%), followed by 9 cases (8.74%) of dysgerminoma, YST (3 cases, 2.91%), MM GCT (3 cases, 2.91%), choriocarcinoma (2 cases, 1.94%) and 1 case (0.97%) of IT. One interesting rare case of MM GCT was composed of mixed malignant GCTs (malignant teratoma, YST, dysgerminoma) arising from gonadoblastoma

component. Other two cases of MM GCT consist of combination of YST and EC. Single case of IT grade 1 was found associated with gliomatosis peritonei.

**Testicular GCT:** Age group of patients varies from one to 55-24 years was the median. Right and left testis was involved in 12 and nine cases, respectively. All 21 patients presented with testicular swelling with associated pain. On gross examination, capsule was intact in all cases. Histopathological examination showed most common tumour type of MM GCT (9 cases, 42.86%) followed by seminoma (5 cases, 23.81%), YST (3 cases, 14.29%) and 2 cases (9.52%) each of EC and MT. Among MM GCT cases, most common histopathological pattern was mixture of malignant teratoma, YST and EC in five cases.

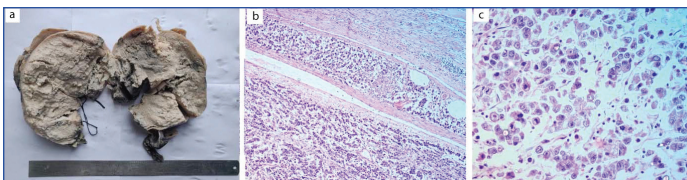
**Extra-gonadal GCT:** Patient's age group varies from four days newborn to 55 years. Total 17 cases were found at extragonadal site, with retroperitoneum (5 cases, 29.41%) being most common site, followed by anterior mediastinum (4 cases, 23.53%), sacrococcyx (3 cases, 17.65%), CNS (2 cases, 11.76%) and one each case (5.9%) of cervical lymph node, cervix and pericardial location. All cases of retroperitoneal and sacrococcygeal mass were MT. Anterior mediastinum showed three cases of seminoma and one case of GCT, Not Otherwise Specified (NOS). The CNS shows one each case of MT and germinoma. One case non gestational choriocarcinoma was present involving cervix. One rare case of germinoma was presented as a pericardial cyst and one case of cervical lymph node GCT was identified without any primary tumour.

Individual type of GCT shows similar histopathological features irrespective of gonadal or extragonadal site. The MT shows variable mixture of mature components arising from ectoderm, mesoderm and endoderm [Table/Fig-3]. Dysgerminoma and seminoma share similar microscopic features revealing nests of monomorphic tumour cells separated by thin fibrous septa containing lymphocytes [Table/Fig-4,5]. Histopathological features of individual components in MM GCT are identical to those in pure forms. The YST shows typical reticular pattern with other pattern being Schiller-Duval bodies, papillary, solid, glandular, polyvesicular vitelline and parietal pattern. The EC is composed of pleomorphic tumour cells with prominent nucleoli arranged in solid, glandular and papillary pattern [Table/Fig-6]. Grading of IT on basis of immature neuroepithelium is done in ovary, but not in testis [Table/Fig-7]. Seminoma of mediastinum shows microscopic findings similar to gonadal counterpart [Table/Fig-8]. The YST may show typical pattern resembling allantoic remnant [Table/Fig-9] and EC often shows foci of lymphovascular tumour emboli [Table/Fig-10].

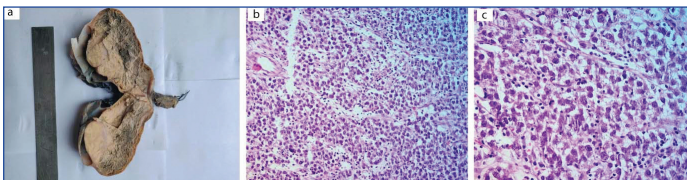


[Table/Fig-3]: Mature Teratoma (MT), Ovary. a) Section shows stratified squamous epithelium with underlying sebaceous gland tissue and mature adipose tissue (H&E, 4x); b) Section shows mature elements of bone tissue, cartilage tissue and salivary gland tissue in background of adipose tissue (H&E, 4x); c) Section shows mature thyroid tissue adjacent to mature cartilage (H&E, 4x); d) Section shows retinal pigment epithelium surrounded by mature glia tissue (H&E, 10x).

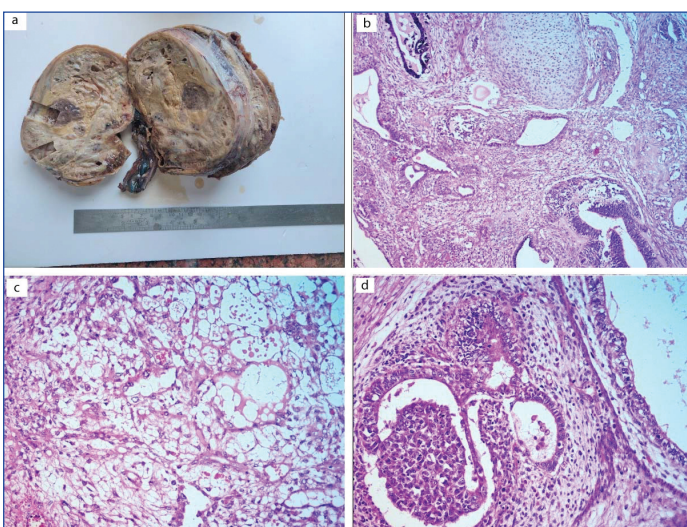




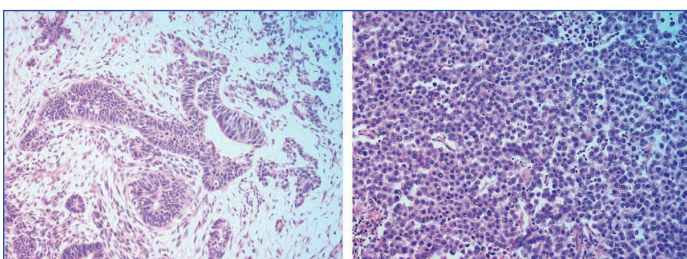
**[Table/Fig-4]:** Dysgerminoma, Ovary. a) Gross specimen showing grey-white homogenous cut surface; b) Low power view showing dysgerminoma cells arranged in cord like pattern with intact ovarian capsule (H&E, 10x); c) High power view showing typical vesicular nuclei and prominent nucleoli of cells in dysgerminoma (H&E, 40x).



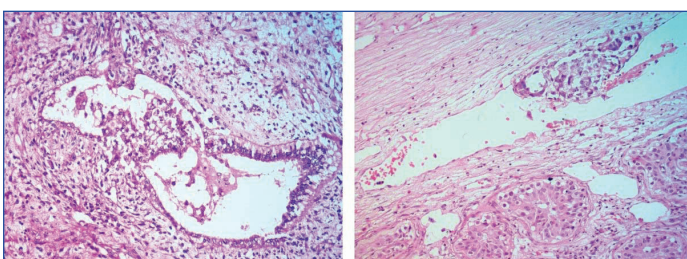
**[Table/Fig-5]:** Seminoma, Testis. a) Gross specimen having grey-white homogenous cut surface; b) Section shows cells arranged in nesting pattern separated by thin-walled fibrous septa. (H&E, 20x); c) High power view showing seminoma cells separated by thin fibrovascular septa containing mature lymphocytes (H&E, 40x).



**[Table/Fig-6]:** Malignant mixed germ cell tumour, Testis. a) Gross specimen of testis showing solid heterogeneous cut surface; b) Low power view having component of malignant teratoma showing, immature neuroepithelium in lower part, immature cartilage and pigmented epithelium in upper part, (H&E, 10x); c) Section shows reticular/microcystic pattern of YST (H&E, 20x); d) Section shows component of EC on left side along with YST component on right side (H&E, 20x).



**[Table/Fig-7]:** Case of Immature Teratoma (IT), ovary showing immature neuroepithelium (H&E, 20x); **[Table/Fig-8]:** Mediastinal mass showing seminoma tumour (H&E, 20x). (Images from left to right)



**[Table/Fig-9]:** Case of YST of ovary showing pattern resembling allantoic remnants (H&E, 20x); **[Table/Fig-10]:** Case of EC showing lymphovascular invasion by tumour cells with adjacent normal testis (H&E, 20x). (Images from left to right)

## DISCUSSION

Gonadal GCT arises from totipotent primordial germ cells, whereas EG GCT originated from displaced primordial germ cells during their migration to testis or ovary [5,11]. The GCT mainly arises from gonads, but about 1-5% of all GCT originates at extragonadal locations [12]. Most common sites for EG GCT in adults are the mediastinum, retroperitoneum and cranium, in descending order. In children, sites for EG GCT are cranium and sacrococcyx [13]. GCT may develop at any age, but children and adolescents are commonly affected. Testicular The GCT usually affects young males aged 20-45 years [14]. Seminoma is more common in 4<sup>th</sup> decade, whereas NSGCT usually show peak incidence in the 3<sup>rd</sup> decade [15]. Mixed malignant GCT in testis has similar clinical attributes as the non seminomatous component they carry [16].

Mature cystic teratoma of ovary usually occur in <50 years female with a peak incidence between 20-29 years. Malignant GCT including IT is mostly seen in children and young women [8,17]. Ovarian GCT usually present with abdominal pain with abdominal mass. About 10% ovarian malignant GCT presented with an acute abdominal pain due to torsion or haemorrhage [18]. Ovarian GCT is usually unilateral, but about 4.4% malignant GCT is bilateral [19]. In present study, ovarian GCT was bilateral in 5.82% cases (6 cases).

In testis, seminoma arises from germinal epithelium of seminiferous tubules [20]. They show well encapsulated mass with solid homogenous cut surface. On morphology, neoplastic cells are similar to GCNIS [21]. The EC present variegated cut surface showing solid white to tan cut surface mixed with necrosis and haemorrhage. Microscopy showing tumour cells with embryonic stem cells resemblance with variable architecture pattern and predominant solid pattern. Nuclear pleomorphism, macronucleoli and nuclear overlapping with frequent mitosis help to differentiate it from YST and seminoma. The YST shows solid cystic cut surface with histology showing variable pattern in different combination. It resembles extraembryonic structures including yolk sac and primitive mesenchyme [9]. The MM GCT is the most common subgroup among NSGCT in the present study, comparable to study done in India and Turkey [22,23]. In MM GCT, EC and YST components are closely associated as in present study [9]. Most common combination in this study is EC with MT and YST.

In ovary, MT shows cystic gross appearance containing sebaceous material, hair and sometimes Rokitansky protuberance. Present study results show MT as most common ovarian GCT similar to study conducted by Lin X et al., [1]. Dysgerminoma is malignant ovarian GCT showing pathological findings comparable to seminoma. Dysgerminoma was the most common type of malignant GCT, whereas Lin X et al., study showing YST as the most common type of malignant GCT [1]. The YST shows morphology similar to testicular YST, showing common patterns of microcystic, endodermal sinus pattern, solid and papillary pattern. Other rare patterns are polyvesicular vitelline, parietal and hepatoid. The EC is rare tumour in ovary in pure form or as a component. The IC comprises <1% of teratoma of ovary, which is predominantly solid on gross in contrast to MT. One rare case report of IT grade I, was showing immature neuroepithelial component [5,8,24-26].

Among EG GCT, mediastinum is the most common site as indicated by Albany C and Einhorn LH however present study shows retroperitoneum as the most common EG GCT site [27]. Regardless of gender, teratoma is most common EG GCT in prepubertal age. Sacrococcygeal teratoma is one of the most common congenital neoplasm [28]. Histopathological features of EG GCT are same as observed in their gonadal counter parts. Sometimes somatic malignancy may develop from EG GCT in a case of Teratoma or mixed EG GCT [29].

Treatment in ovarian malignant GCT includes comprehensive surgical excision consisting of hysterectomy, bilateral salpingo-oophorectomy, omentectomy and pelvic lymphadenectomy. Patients

with dysgerminoma stage IA and IT grade 1 may be treated with fertility sparing unilateral salpingo-oophorectomy. All patients undergo adjuvant chemotherapy except stage IA dysgerminoma and grade 1 IT [25,30]. Testicular GCT and EG GCT are managed with surgical excision with adjuvant radiotherapy and chemotherapy [4,10,31].

## Limitation(s)

Limitations of study include lack of immunohistochemistry and radiological features. Future studies on GCT are required to draw out comparison between clinicopathological findings and patients' outcome after management.

## CONCLUSION(S)

Till date, very few studies have been conducted in India comprising of GCT of gonadal and extragonadal sites. So, the present study was carried out to manifest variable histological types of GCT, diverging according to age of patient and site of origin. Definite histopathological diagnosis and accurate histological typing plays a crucial role in determining the further treatment. In cases of mixed GCT, proportion of each component should be mentioned in final pathological report, as tumour prognosis in such cases will be on par with the predominant component.

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