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Original Article

Survival outcomes and prognostic factors of extragonadal germ cell tumors: An institutional experience over a decade

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Abstract

Background: Extra gonadal germ cell tumors (EGCT) are rare tumors with late presentation to the oncologist. Though they respond well to chemotherapy, cure is compromised in the real world due to various factors. This study was undertaken to assess the clinical profile, survival outcomes and factors effecting outcomes of extragonadal germ cell tumors in men.

Patients and Methods: This is a retrospective study of male extra gonadal germ cell tumors diagnosed and treated from January 2011 to December 2021. Patient demographics, tumor characteristics and treatment details were retrieved from case records.

Statistical analysis: Kaplan–Meier estimates of survival was used for survival analysis. Cox regression model was used to analyze the prognostic factors using SPSS version 25.

Results: A total of 32 patients were analyzed. The median age at presentation was 26 years (range:13–40years). Primary site of the disease was mediastinal in 25patients (78%), retroperitoneal in 4(12%) and intracranial in 3patients (10%). Histology was non seminomatous in majority of mediastinal tumors (15 patients (60%)) while all the retroperitoneal tumors were non seminomatous. Ninety four percent of the patients completed the planned cycles of chemotherapy. BEP was the most common chemotherapy regimen used (n–21 ,65%). Post chemotherapy residual disease was present in 13 patients (10 nonseminomatous, 3 seminomatous), who underwent surgery (9 patients) and radiotherapy (3patients). Median time to relapse was 8 months (range 1–11). Univariate analysis showed that nonseminoma histology, mediastinal site, post chemotherapy elevated tumor markers, Eastern Cooperative Oncology Group performance status (ECOG PS) more than 2, poor risk on International Germ Cell Cancer Collaborative Group (IGCCCG) risk stratification were associated with inferior outcomes. On multivariate analysis, non–seminoma histology, mediastinal site, ECOG PS >2 and IGCCCG poor risk were associated with statistically inferior OS. At a median follow up of 65 months (range 1–132 months) 2–year PFS and OS were both 100% in seminoma and both 65% in non–seminoma.

Conclusions: Mediastinum is the most common site of EGCT. Site of the primary, non–seminoma histology, poor performance status and poor risk disease are factors contributing to inferior outcome and high mortality. Early medical attention and newer salvage therapies for refractory disease are needed to improve the survival of these patients.

Keywords: extragonadal germ cell tumor, mediastinal germ cell tumor, non–seminoma, retroperitoneal germ cell tumor

Introduction:

Extra gonadal germ cell tumors (EGCT) are rare tumors representing up to 5% of all germ cell tumors (GCTs) with an incidence around 1/1,000,000[1]. It was hypothesized that EGCTs are either a consequence of a mis migration of germ cells along the urogenital ridge during embryogenesis or result from germ cells that are distributed physiologically to the liver, bone marrow, and brain to provide regular functions or convey hematologic or immunologic information. [2]

The clinical and biological features of extragonadal germ cell tumors that are similar to gonadal germ cell tumors are a) occurrence in young adults, b) midline locations, c) metastasis to lung, liver and bone, d)

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seminoma and nonseminoma histological subtypes, e) elevated serum tumor markers (beta human chorionic gonadotropic hormone, β–HCG, alfa–fetoprotein, AFP), f) isochromosome i(12p) karyotypic abnormality and g) sensitivity to cisplatin–based combination chemotherapy. Features distinct from gonadal germ cell tumors are a) increased tumor bulk at presentation, b) high frequency in patients with Klinefelter's syndrome and c) high frequency of development of hematological malignancies (mediastinal primaries only). [2] It may be difficult to distinguish extragonadal tumors from metastatic tumors where the primary testicular lesion has regressed. For example, in some cases a scar is found in the testis probably representing a 'burn–out' or 'auto infarcted' primary. [3]

Primary surgery is not effective in EGCT except in mature teratoma. Literature supports cisplatin–based chemotherapy followed by consolidative local therapy with surgery or radiotherapy. [4–9]

The purpose of this article is to share our institutional experience with this rare disease, with emphasis on the clinical spectrum, survival outcomes and factors effecting outcomes.

Patients and Methods:

This is a retrospective study of men treated in our institute from January 2011 to December 2021. Permission from the institutional ethics committee was obtained prior to start of the study. The diagnosis of EGCT was made based on a histologically proven GCT arising in the mediastinum, retroperitoneum or other site, without demonstrable testicular abnormalities, as determined by a physical examination and testicular ultrasonography. Patients were classified as nonseminomatous GCT if an elevation of serum AFP greater than 10 ng / ml or serum β–HCG greater than 100 IU / liter was found, even when a histopathological examination showed pure seminoma. Risk stratification was done as per IGCCCG classification. [10]

Patient demographics, tumor characteristics and treatment details were retrieved from case records. Factors like histology, site of primary, risk group, chemotherapy regimen used and post chemotherapy markers status were analyzed for their impact on survival. Survival status was confirmed through outpatient follow–up records and telephonic conversation. Categorical data was presented as frequencies and percentages. Chi–square test / Fisher's exact test was used to compare the categorical data. The data on continuous variables like the age, was expressed as mean with standard deviation or median with range. Cox regression model was used to analyze the prognostic factors. Kaplan–Meier method was used to estimate progression–free survival (PFS) and overall survival (OS). Progression–free survival (PFS) is defined as the time from diagnosis to disease progression or death due to any cause. Overall survival (OS) is defined as the time from diagnosis to death due to any cause. Response assessment was done using RECIST version 1.1. All statistical analysis were carried out at 5% level of significance and P value < 0.05 considered statistically significant using SPSS version 25. [11]

Results:

A total of 32 patients were analyzed. Median age of presentation was 26 years (range 14–40 years). Eastern Cooperative Oncology Group performance status (ECOG PS) was > 2 in 18 patients, </= 2 in 14 patients. Duration of symptoms ranged from 1 month to 12 months with a median duration 2 months. In patients with mediastinal EGCTs, the most common symptoms at presentation were shortness of breath (70%), chest pain (60%), vena cava occlusion syndrome (40%), fatigue (25%) and weight loss (25%). Less frequent symptoms were hemoptysis, hoarseness of voice, and dysphagia (4% each). Abdominopelvic pain (75%) and back pain (75%) were the most common presenting symptoms in patients with retroperitoneal GCT. Headache was the most common symptom in intracranial GCT (66%) followed by constitutional symptoms (33%). One patient with mediastinal seminoma had undescended testis and he underwent orchiopexy at 4 years of age. ECOG PS > 2 in 18 patients (56%). The initial diagnosis was achieved by a combination of computed tomography scans, sonograms and tumor markers. Twelve patients underwent upfront biopsy.

Histological characteristics of the patient are shown in Table 1. Mediastinum was the most common primary site (n–25,78%) followed by retroperitoneum (n–4,12%) and intracranium (n–3,10%). Majority of the mediastinal primaries (n–15,60%) and all retroperitoneal primaries (n–4,100%) were NSGCTs. Amongst the 3 intracranial

1) Seminoma/nonseminoma	Total =32
Seminoma	N=12
Nonseminoma	N=20
2) Nonseminoma histology	
Mixed	N=7(35%)
Yolksac	N=3(15%)
Teratoma	N=2(10%)
Embryonal	N=1(5%)
Choriocarcinoma	N=1(5%)
Unclassified	N=6(30%)

Table 1: Histological characteristics of all patients

primaries, one was nonseminoma (33%). All the patients received chemotherapy out of which 2 patients were not able to complete chemotherapy (6%) because of sepsis related mortality. Chemotherapy protocols have been detailed in table 2. All the 3 intracranial primary tumors received chemotherapy and craniospinal irradiation (25 Gray CSI followed by cranial boost of 21 Gray with a total of 42 Gy). Of the 15 mediastinal NSGCTs. 9 patients had residual disease post chemotherapy, for which surgery was done in 6 patients, radiation in 2 patients and one patient defaulted. Amongst the 6 patients who underwent surgery, postop histopathology was teratoma in 3, necrosis in 1 and residual tumour in 2 patients. Patients with residual disease were given 2 cycles of EP or VIP.

1) 1ST line regimens used	
BEP	N=21(66%)
VIP	N=8(25%)
EP	N=2(6%)
TIP	N=1(3%)
2) >/=2nd line regimens used	
TIP	N=5
VeIP	N=1
Gemcitabine +docetaxel	N=1
3) Post chemotherapy residual disease Mediastinal	Total =13
Seminoma	N=3 (2–Good risk,1–Intermediate risk)
Non seminoma	N=9 (9–Poor risk)
Retroperitoneal	
Nonseminoma	N=1 (Intermediate risk)
4) Post chemotherapy residual treatment	
Surgery	N=8 (Seminoma–2, Nonseminoma –6)
Radiation	N=3 (Seminoma–1, Nonseminoma–2)
Defaulted	N=1
5) Postop HPE	
Teratoma	N=3 (nonseminoma–3)
Necrosis	N=3 (seminoma–2, nonseminoma–1)
Residual tumor	N=2 (nonseminoma–2)
6) Cause of death	Total =7
Treatment related mortality	N=2 (Mediastinal non–seminoma –2)
Post surgery residual disease refractory to salvage regimens	N=2 (Mediastinal non–seminoma –2)
Relapsed disease refractory to salvage regimen	N=2 (Retroperitoneal nonseminoma –1, mediastinal non–seminoma –2)
Defaulted	N=1(mediastinal nonseminoma)

Table 2: Treatment details of patients (N–number, S–seminoma, NS– nonseminoma, BEP (Bleomycin, Etoposide, Cisplatin), VIP (Etoposide + Ifosfamide +Cisplatin), EP (Etoposide, Cisplatin), TIP (Paclitaxel + Ifosfamide +Cisplatin), VeIP (Vinblastine, Ifosfamide, Cisplatin).

All mediastinal seminomas except one were good risk (n–9 ,90%) and all underwent chemotherapy with post chemo residual disease seen in 3 cases who underwent surgery (2 patients) and radiation (one patient). Postoperative histopathology report in both the patients was suggestive of necrosis

Treatment related mortality due to sepsis was seen in 2 patients (6%). Neutropenia was the most common acute toxicity, with grade 3 toxicity seen in 9 patients (28%). Neuropathy of any grade was seen in 8 patients (25%).

Four patients relapsed (1–retroperitoneal nonseminoma intermediate risk and 3–mediastinal nonseminoma) of which 3 received second line chemotherapy and 1 defaulted. Median time to relapse was 8 months (range 1–11). All the patients who relapsed, progressed and succumbed to death. Salvage regimens and treatment related outcomes are shown in table 2.

Survival analysis: Univariate and multivariate analysis

Median duration of follow up is 65 months (2–132 months). Of the 32 patients, 7 patients expired all of whom were with poor performance status (ECOG PS >2) and from mediastinal site. Two deaths were due to treatment related mortality (1–firstline ,1–second line), 2 due to primary refractoriness to first line therapy and 3 were due to early relapse with no response to salvage chemotherapy.

At a median follow up of 65 months, 2–year PFS and OS of all the patients was 78%. The 2–year PFS and OS of seminoma (both 100%) was superior compared to nonseminoma (both 65%) which was statistically significant (p–0.023) (figure 1). Presence of yolk sac and choriocarcinoma components was associated with poor prognosis though not statistically significant (2–year OS 77% versus 54%, p–0.06). The 2–year PFS and OS was inferior in mediastinal nonseminoma compared to other sites (53% versus 94%, p<0.001). There is no difference in survival based on chemotherapy regimen used (p–0.7). The 2–year OS was superior in patients who achieved tumor markers normalisation post chemotherapy compared to patients who had elevated tumor markers post chemotherapy (>=S1), 94% versus 50% (p–0.04). ECOG PS >2 was associated with statistically significant inferior survival (55% versus 94%, p–<0.001). Two–year OS was 100% ,75% and 50% in good risk, intermediate risk and poor risk categories respectively (p–0.003) (figure–2). All these factors which were statistically significant on univariate analysis were tested on multivariate analysis using logistic regression. On multivariate regression non–seminoma histology (p–0.04), mediastinal nonseminoma (p–0.002), ECOG PS >2(p–0.04), EGCCCG poor risk (p–0.01) were associated with statistically inferior OS. Post chemotherapy tumor marker elevation lost significance on multivariate analysis (p–0.1).

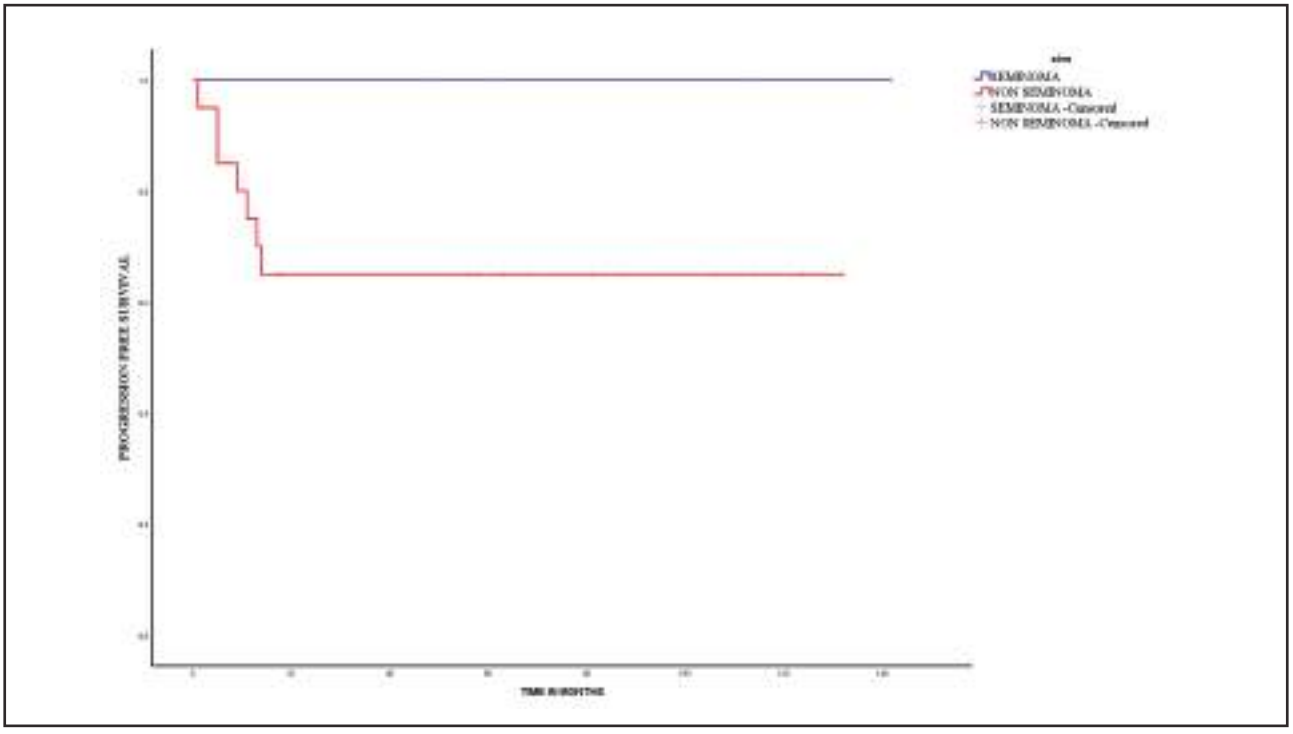


Figure 1A: Showing progression free survival (PFS) in 1) Seminoma and 2) Nonseminoma with 2–year PFS 100 % versus 65% respectively (p–0.024).

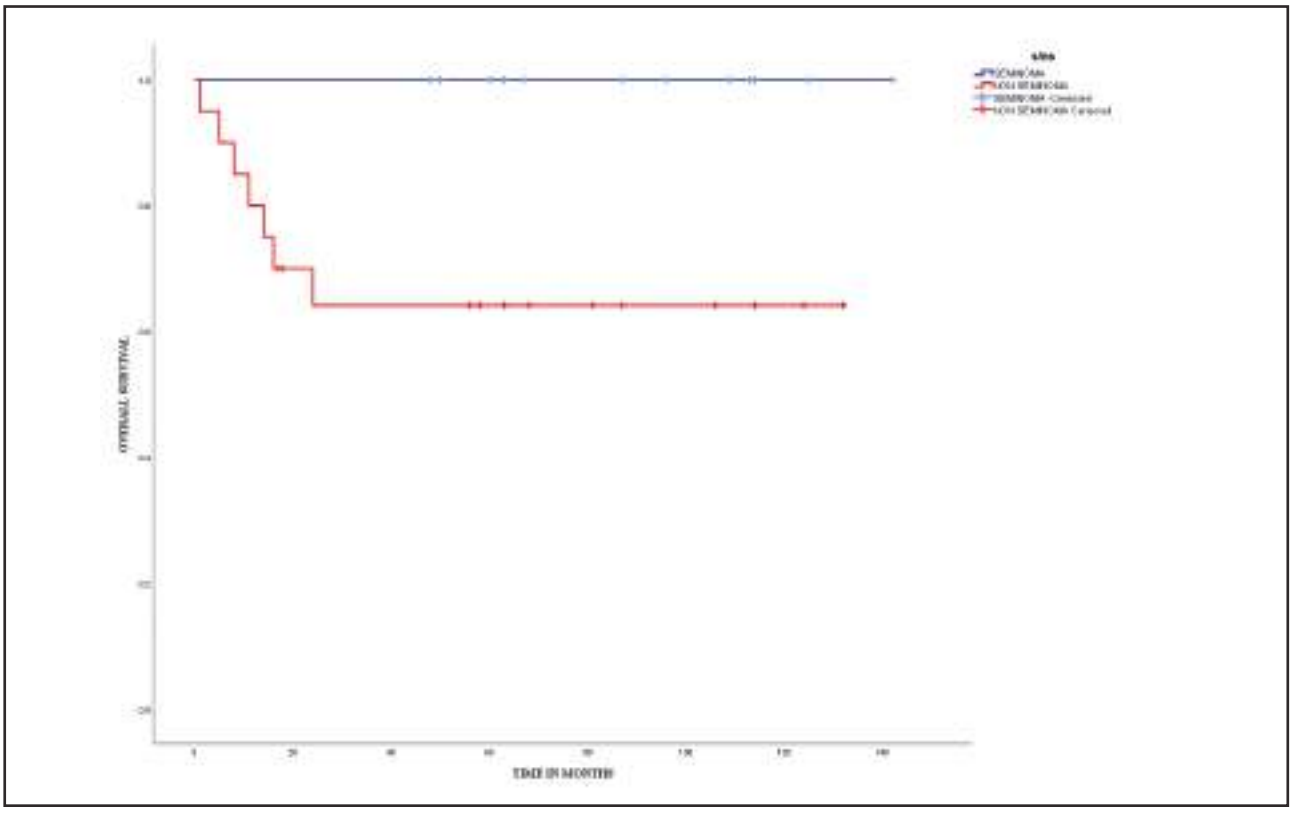


Figure 1B: Overall survival (OS) in 1) Seminoma and 2) Nonseminoma with 2–year OS 100 % versus 65% respectively (p–0.024).

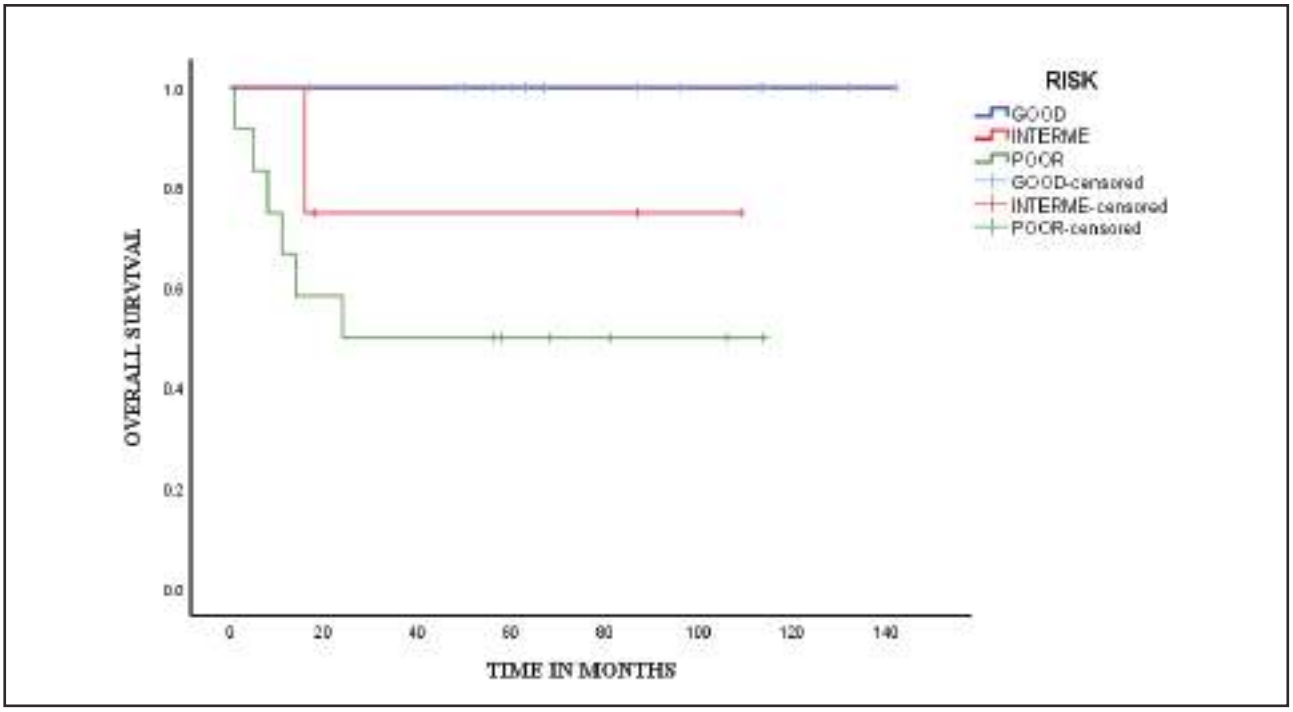


Figure 2: Overall survival according to IGCCCG risk .1= Good risk ,2=Intermediate risk, 3=Poor risk with 2–year OS 100%,75% and 50% respectively (p–0.003).

Discussion

Extragonadal germ cell tumors are rare in the spectrum of germ cell tumors and their outcomes are not studied commonly. Though testicular germ cell tumors have high cure rates, survival of patients with EGCTs is still low. One possible explanation for low cure rates is delay in presentation as the symptoms are nonspecific. Diagnosis of EGCT is possible only with high index of suspicion.

The median age of presentation in our study was 26 years which is slightly younger compared to western world of 30 years [12,14] and similar to other Indian studies. [13] There is not much difference in the median age in patients with seminoma and nonseminoma, 27 versus 25 years, while there was slight late age peak in seminoma in other studies. Most of the studies on EGCT included only retroperitoneal and mediastinal primaries but our study included intracranial primaries also. The most common presenting symptoms were shortness of breath and chest pain in mediastinal tumors, abdominopelvic pain and backache in retroperitoneal tumors, and headache in intracranial primary, which was similar to other studies. [4,7,12,14] Superior Vena Cava (SVC) syndrome was present in 40% of the mediastinal EGCT in this study which is higher than other studies (10–20%) owing to late presentation. [12,13,14]

Mediastinum was the most common site in this study which is comparable to other Indian studies, [13] but is in contrast to the study by Bookmeyer at al [12] where both mediastinum and retroperitoneum were having equal distribution. Non seminoma was the most common subtype similar to other studies. [13] ECOG PS >2 was present in 12 patients (37%) which was seen in majority of patients with poor risk as per IGCCCG[20]. Mixed histology was the most common subtype in non–seminoma followed by yolk sac which is similar to other studies. [12,13,14]

Treatment related mortality was seen in two patients. These patients presented in poor performance status and couldn't complete the planned therapy. This highlights the importance of performance status in the clinical management of EGCTs. Also, all the patients who relapsed, succumbed to death. This clearly indicates that first treatment needs to the best and drug doses should never be compromised during treatment. Patients need to be educated on the importance of compliance to therapy and strict adherence to treatment protocols.

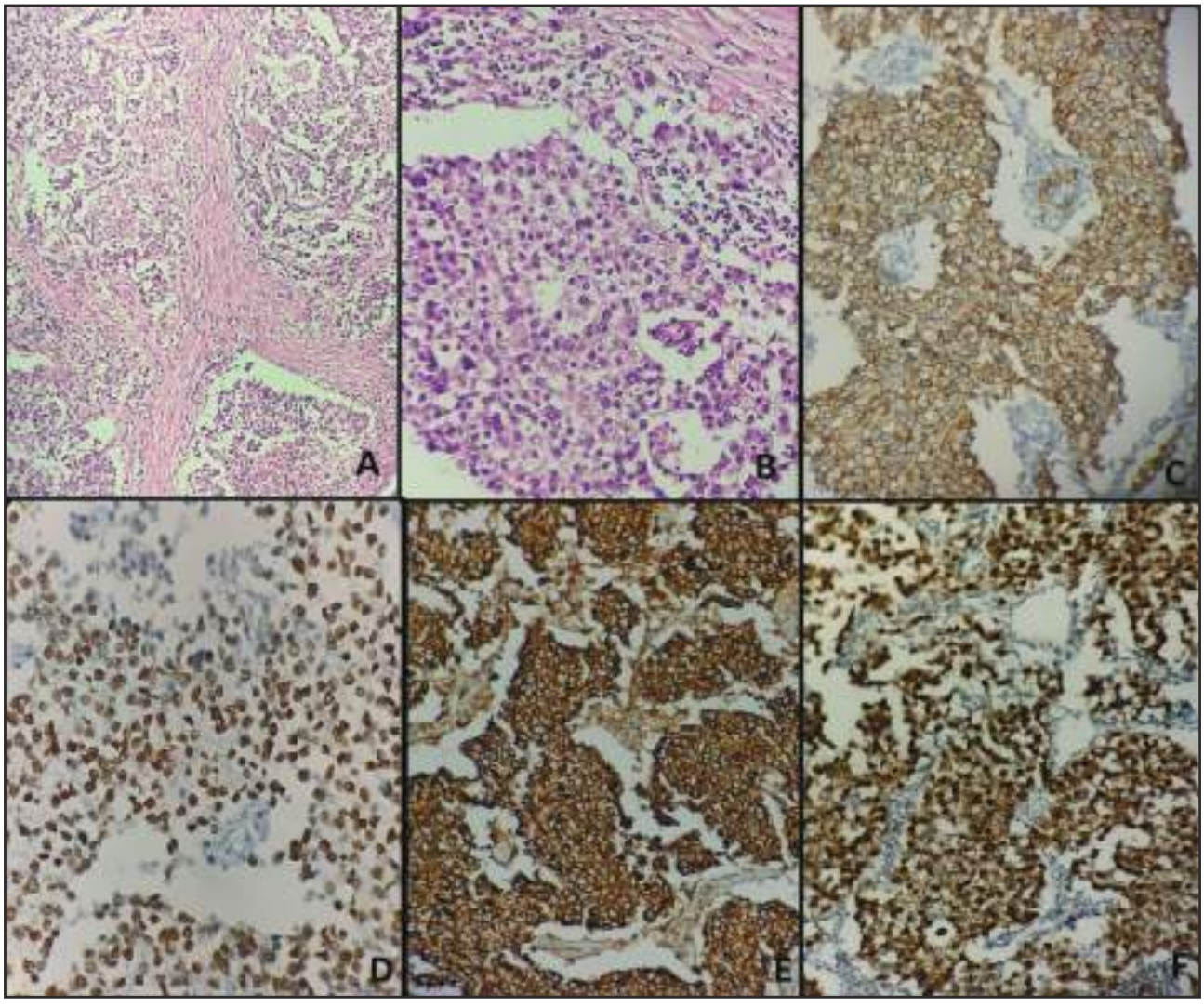


Figure 1: Seminoma A and B. Sheets of polygonal cells separated by fibrous septae containing lymphocytes. (H&E x 100 and 400), Tumor cells are positive for (C) CD117 ,(D) SALL4 (E) OCT3/4 7and (F) PLAP

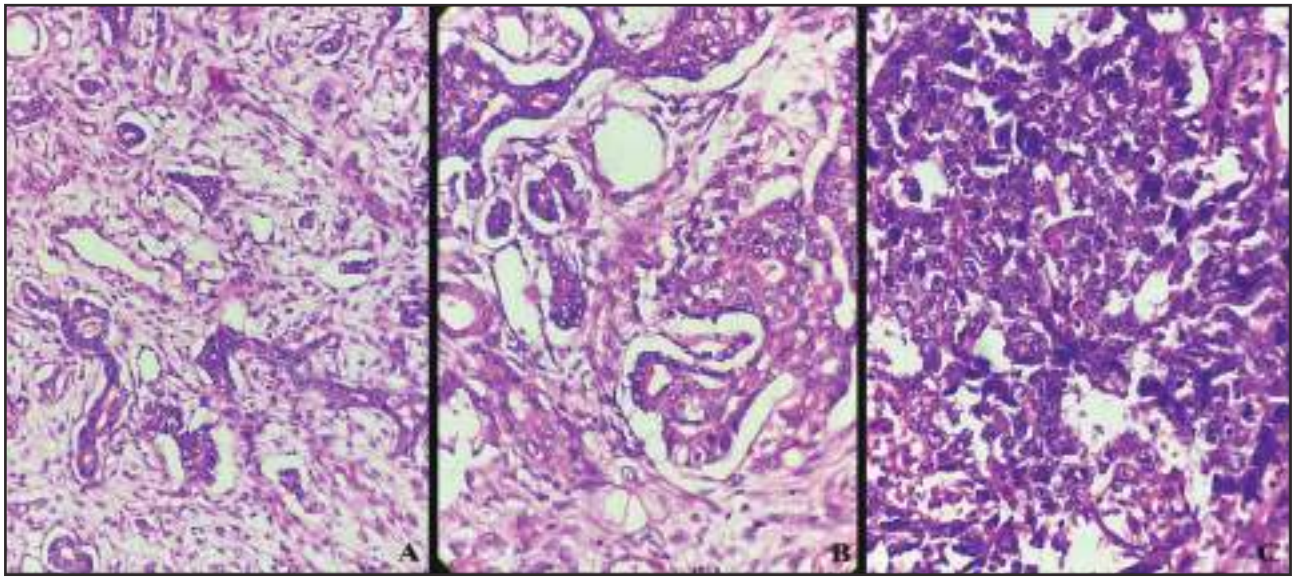


Figure 2: Non seminomatous germ cell tumor with (A and B) yolk sac (H&E x 100 and 400); (C) embryonal component (H& E x400)

The 2–year OS of extragonadal seminoma in our study (100%) was similar to the survival rate of seminoma in other studies. [12,13,14] The 2–year OS rate of non–seminomas in our study was comparatively more (65%) than the OS rate in older studies (45%). The survival rates of intracranial germ cell tumors were equal to other studies of intracranial germinoma with 2–year OS of 100%. [15–17] Though the survival rates of seminoma are 100 percent, survival rates of non seminomatous tumors are low, highlighting the need for aggressive management of these tumors.

Statistical analysis showed that performance status, histology, primary tumor site and IGCCCG risk category are associated with survival outcomes. All these are non–modifiable factors except performance status which can be improved with early diagnosis and good supportive care. Unlike testicular germ cell tumors where diagnosis can be made on clinical examination, extragonadal tumors need high index of suspicion for early diagnosis.

Conclusion:

Mediastinum is the most common site of EGCT. Site of the primary, non seminomatous histology, poor performance status and poor risk disease are factors contributing to inferior outcome and high mortality. High index of suspicion, prompt diagnosis, strict adherence to treatment protocols along with good supportive care are essential in the management of these patients.

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Funding and Conflict of Interest:

Nil

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