# Disease characteristics and survival outcomes of extragonadal primary germ cell tumour in two Canadian tertiary cancer centres

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## Abstract

**Introduction:** Extragonadal germ cell tumours (EGCTs) are a heterogeneous group with distinct natural history and responses to treatment modalities. We sought to evaluate characteristics and survival outcomes in men with EGCTs.
**Methods:** We performed a retrospective analysis on a consecutive list of men diagnosed with EGCT in two Albertan cancer centres between 1990 and 2013. Demographic characteristics and outcomes, stratified by primary site, were evaluated.
**Results:** Sixty-nine cases were identified. The median age was 29 (range 15–76) and 48 cases (70%) were non-seminomatous. Twenty-four (35%) belonged to International Germ Cell Cancer Collaborative Group (IGCCCG) favourable risk group, 14 (20%) to intermediate, and 31 (45%) to poor. Thirty (43%) had mediastinal primary (MPs); 29 were treated with first-line bleomycin, etoposide, and cisplatin (BEP). Seventeen (57%) relapses occurred, of which three patients achieved long-term survival. Seventeen (25%) had a central nervous system (CNS) primary, with eight (47%) classic germinoma. Seven (41%) received primary chemotherapy alone; 5 (29%) received primary radiotherapy alone, and 5 (29%) received both. Nineteen (28%) had a retroperitoneal primary (RPs) and received first-line chemotherapy; all but two received BEP and eight (42%) had surgical resection. Three (5%) had other or unknown primary. Five-year overall survival (OS) and disease-free survival for all patients were 56% and 44%, respectively; for MPs, 44% and 34%; for CNS primary, 76% and 53%; for RPs, 58% and 53%. Factors that correlated with decreased OS were elevated alpha fetoprotein (AFP) (p<0.001) or human chorionic gonadotropin (HCG) (p=0.001), lactate dehydrogenase (LDH) levels (p=0.028), bone metastasis (p<0.001), lung metastasis (p<0.001), and IGCCCG poor risk (p=0.001).
**Conclusions:** EGCT is a rare, but important subset of GCT. Patients with EGCTs, despite aggressive treatments, still have poorer outcomes than gonadal primary.

## Introduction

Extragonadal germ cell tumours (EGCTs) comprise a heterogeneous group of primary germ cell tumours with distinct natural history and responses to different treatment modalities. The incidence of EGCTs is estimated at 1.9–3.4/1 000 000.[1] EGCTs often occur in the midline of the body, with the three most common sites in the anterior mediastinum, retroperitoneum, and pineal gland.[1,2] Epidemiologic studies suggest that although similar in morphologic appearance, the embryonic and genetic initiating events of EGCTs may be distinct from the gonadal germ cell tumours (GGCTs).[1-4] EGCTs, especially of the mediastinal origin, are often marked by inferior survival outcomes compared to GGCTs, as well as hematologic neoplasms (acute myeloid leukemia and malignant histiocytosis) and systemic mast cell disease that are unrelated to treatment effect.[5,6]

The usual treatment for EGCTs has been platinum-based chemotherapy regimen, such as bleomycin, etoposide and cisplatin (BEP), followed by surgical resection of residual tumours, if feasible.[7] Previously published retrospective studies have suggested efficacy of chemotherapy in achieving complete response and long-term survival in both seminomatous and non-seminomatous germ cell tumours of extragonadal origin.[8-12] Patients with relapse can be salvaged with high-dose chemotherapy with stem cell support similar to disease relapse in GGCTs, although prospective, randomized data are lacking.[13,14] There is substantial variability in the case volume and surgical expertise among centres and a multidisciplinary care in a specialized tertiary cancer centre is essential in the treatment of EGCTs.[7,15] Even with optimal treatments, survival varies among different primary sites and can range from five-year survival of 30–40% in the mediastinal EGCTs to 90% in germinoma of the central nervous system.[4,11,16,17] To date, however, published data on the treatment of EGCTs in Canadian patients are scarce.

The objectives of our study were to evaluate patient, disease, and treatment characteristics and survival outcomes in male patients diagnosed with EGCTs in two Canadian tertiary cancer centres.

## Methods

We performed a retrospective analysis on a consecutive list of all male patients diagnosed with EGCT and treated in Alberta. All cases of GCTs in the two tertiary cancer centres (Tom Baker Cancer Centre, Calgary, AB; Cross Cancer Institute, Edmonton, AB) were reviewed; all consecutive cases in which treating physicians made the diagnosis of and proceeded with treatments for EGCT were included. All cases underwent attempts at pathologic diagnosis with either fine-needle, core-needle or excisional biopsy; 17 patients had non-diagnostic pathology and were diagnosed and treated as EGCT based on tumour markers or clinical presentation. Electronic and paper charts were obtained and reviewed by the study coordinators using the pre-specified data template. Data for patients treated in Edmonton were only available between January 1, 2002 and December 31, 2010, while all data were accessible for patients treated in Calgary between January 1, 1990 and December 31, 2013. Disease relapse was determined if there was a rise in tumour markers or radiologic progression after the first-line curative therapy was finished; post-chemotherapy resection of residual tumour was considered to be part of the first-line therapy and was not counted as relapse.

Data were transferred from Excel to Stata S/E Version 13 for analysis. Categorical variables were expressed as a frequency and percentage; patient age was expressed as mean and range. Overall survival (OS) was defined as the date of diagnosis to the date of death or last followup visit, with patients censored at their last followup visit. Disease-free survival (DFS) was defined as the date of diagnosis to the date of relapse, progression, death, or last followup visit and similarly censored at last followup visit. OS and DFS curves in the entire cohort and the following subgroups, stratified by the primary site, were estimated by Kaplan-Meier method with log-rank test to compare the differences among central nervous system (CNS), mediastinal (MP), and retroperitoneal primary (RP) sites. Hazard ratios for the risk group stratification (e.g. International Germ Cell Cancer Collaborative Group [IGCCCG]) were modeled by univariate Cox regression. A p value <0.05 was considered to be statistically significant.

## Results

Between 1990 and 2013, 69 patients in two Albertan tertiary cancer centres were diagnosed with EGCT. Table 1 summarizes patient, disease and treatment characteristics for all patients, as well as three subgroups stratified by primary site.

Among 30 patients (43%) with MPs with ≥5 years of followup, 5/8 patients (63%) with seminomatous and 6/19 (32%) with non-seminomatous MPs achieved long-term survival. One patient died due to bleomycin lung toxicity after two cycles of BEP. Upfront or salvage high-dose chemotherapy with autologous stem cell support was used in 11 patients, of which three (27%) survived ≥5 years. Seventeen (57%) relapses occurred; most were high-risk (n=2, 13%) or very high-risk (n=15, 87%) by the IGCCCG2 criteria.[18] Fifteen (88%) received salvage chemotherapy with (n=1) or without (n=14) radiation therapy (RT), most commonly paclitaxel, ifosfamide and cisplatin (TIP) (n=8). Other regimens included upfront salvage high-dose chemotherapy with stem cell support (n=3), BEP (n=2), and vinblastine, ifosfamide and cisplatin (VeIP, n=2). Two patients had resection of residual mass after salvage therapy, all of which contained viable non-teratomatous GCTs. Three patient (20%) with relapse achieved long-term survival.

Seventeen patients (25%) had a CNS primary, of which eight (47%) were classic germinoma; five (29%) had IGCCCG intermediate- or poor-risk disease. Seven (41%) received primary chemotherapy alone; five (29%) received primary RT alone; five (29%) patients received both. Among those with ≥5 years of followup, 6/7 patients (86%) with CNS germinoma and 5/8 (63%) with non-seminomatous CNS primary achieved long-term survival. One patient passed away due to possible bleomycin lung toxicity five months after BEP regimen. Five patients (29%) relapsed, of whom three patients (60%) achieved long-term survival.

Nineteen patients (28%) had a RP. Five (26%) were accompanied by other visceral or mediastinal lymph node metastases. Most (n=15, 79%) had non-seminoma. All received first-line chemotherapy; all but two received BEP. Eight (42%) patients had upfront or salvage surgical resection, seven of which were found with viable tumour. All eight patients (42%) who relapsed had non-seminoma and died within one year of relapse. None of the RP patients received salvage high-dose chemotherapy with autologous stem cell support at the time of the first recurrence; only one patient received salvage high-dose chemotherapy after salvage chemotherapy failure, but eventually died from relapse. The most common salvage therapy was TIP (n=3), followed by VeIP (n=2), etoposide (EP) (n=1), and upfront salvage high-dose chemotherapy with stem cell support (n=1).

Lastly, three patients (5%) had other (n=1 for prostate, n=1 for intraperitoneal) or unknown primary (n=1). The patient with the prostate seminomatous primary achieved long-term complete remission (CR) after first-line chemotherapy, while the other two passed away despite treatment.

The Kaplan-Meier curves of OS and DFS, stratified by the IGCCCG risk groups, are shown in Fig. 1. One patient is excluded for losing followup information. The five-year

**Table 1: Patient, disease, and treatment characteristics of the overall cohort and stratified by primary site**

| Variable | Overall (n=69) | Mediastinal (n=30) | CNS (n=17) | Retroperitoneal (n=19) |
|---|---|---|---|---|
| Age (range) | 29 (15–76) | 29 (16–55) | 21 (15–51) | 39 (21–76) |
| **IGCCCG risk groups** | | | | |
| Favourable | 24 (35%) | 0 | 12 (71%) | 10 (53%) |
| Intermediate | 14 (20%) | 9 (30%) | 1 (6%) | 4 (21%) |
| Poor | 31 (45%) | 21 (70%) | 4 (23%) | 5 (26%) |
| **Tumour characteristics** | | | | |
| Seminoma | 21 (30%) | 9 (30%) | 8 (47%) | 4 (21%) |
| Non-seminoma | 48 (70%) | 21 (70%) | 9 (53%) | 15 (79%) |
| Primary tumour size, median in cm (range) | 9 (1.5–26) | 12 (5–22) | 3 (1.5–4) | 10 (2–26) |
| **Tumour markers** | | | | |
| Elevated alpha-fetoprotein | 23 (33%) | 17 (57%) | 3 (18%) | 3 (16%) |
| Elevated beta-human chorionic gonadotropin | 22 (32%) | 13 (43%) | 1 (6%) | 7 (37%) |
| Elevated lactate dehydrogenase | 22 (32%) | 12 (40%) | 4 (23%) | 6 (32%) |
| **Treatments** | | | | |
| Surgical resection | 25 (36%) | 15 (50%) | 2 (12%) | 8 (42%) |
| First-line chemotherapy | 64 (93%) | 30 (100%) | 12 (71%) | 19 (100%) |
|   BEP | 53 (77%) | 29 (97%) | 5 (29%) | 17 (89%) |
|   Bleomycin lung toxicity | 10/53 (19%) | 4/29 (14%) | 1/5 (20%) | 4/17 (24%) |
| First-line RT | 15 (22%) | 3 (10%) | 10 (59%) | 2 (11%) |
| **Relapse** | | | | |
| Patients with relapse | 32 (46%) | 17 (57%) | 5 (29%) | 8 (42%) |
| Prognostic score at relapse (IGCCCG2)[18] | | | | |
|   Very low | 0 | 0 | 0 | 0 |
|   Low | 1 (3%) | 0 | 0 | 1 (13%) |
|   Intermediate | 5 (16%) | 0 | 2 (40%) | 3 (37%) |
|   High | 4 (12%) | 2 (12%) | 2 (40%) | 0 |
|   Very high | 22 (69%) | 15 (88%) | 1 (20%) | 4 (50%) |
| Treatments | | | | |
|   Salvage chemotherapy | 25 (78%) | 15 (88%) | 2 (40%) | 7 (88%) |
|   Salvage radiation therapy | 8 (25%) | 3 (18%) | 2 (40%) | 2 (25%) |
|   High-dose chemotherapy with autologous stem cell support | 6 (19%) | 5 (29%) | 1 (20%) | 0 |

BEP: bleomycin, etoposide, and cisplatin; IGCCCG: International Germ Cell Cancer Collaborative Group; RT: radiation therapy.

OS (5YOS) and DFS (5YDFS) for all patients were 56% and 44%, respectively. The 5YOS and DFS for MPs were 44% and 34%, respectively; for CNS primary, 76% and 53%; for RPs, 58% and 53% (Fig. 2). Significant differences among the 5YOS (p=0.006) and 5YDFS (p=0.002) were noted among different primary sites, with the CNS primary showing the best survival and MP, worst. The factors that correlated with OS were elevated alpha fetoprotein (AFP) (p=<0.001) and/or human chorionic gonadotropin (HCG) levels (p=0.001), lactate dehydrogenase (LDH) levels (p=0.028), lung metastasis (p=<0.001), bone metastasis (p=<0.001), and IGCCCG risk group (p=0.001).

## Discussion

To the authors' knowledge, our study comprises the largest published Canadian cohort of patients with EGCTs to date.

Goss et al previously published a single-institution experience of 37 patients with EGCTs treated in a tertiary cancer centre in Toronto, ON.[19] The six-year OS for seminomatous EGCTs was 88%, while for non-seminomatous EGCTs, 53%. Our study shows a comparable results in all subgroups except in seminomatous MPs, with lower than expected 5YOS of 63%. Among the nine cases of seminomatous MPs in our cohort, three cases underwent resection of residual disease, which were fibrosis and/or necrotic tissues; four cases relapsed afterwards. This finding, despite the small number of patients, is unusual in gonadal seminoma. This may reflect inherent chemoresistance of MP-GCTs; however, unlike gonadal GCTs, in which orchiectomy specimens are obtained, tissue biopsies in MP-GCTs are typically inadequate and prone to potential sampling issues. Therefore, one hypothesis is that there is some degree of misclassification of non-seminoma into seminoma. While the same may be true for other EGCTs, we did
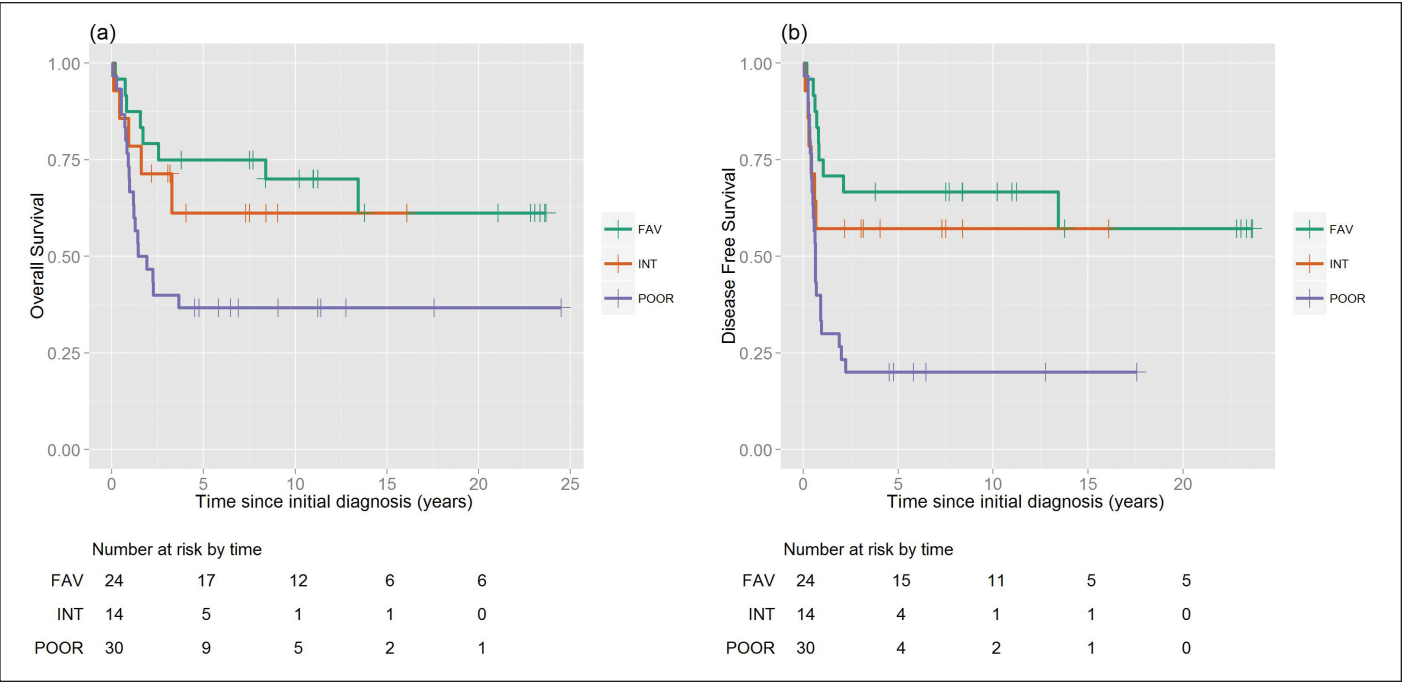
**Fig. 1.** Kaplan-Meier curve of **(a)** overall survival and **(b)** disease-free survival, for the overall cohort. X-axis in months; FAV: IGCCCG favourable risk group; INT: intermediate risk group; POOR: poor risk group.

not note significant discrepancy between our outcomes and those reported in the literature for other primary sites when stratified by seminoma vs. non-seminoma except in MPs.

Our results showed that the outcomes of EGCTs remain inferior to those of GGCTs, even in RP and CNS primary.

This is contrary to other smaller studies that show generally favourable prognosis for RP and CNS GCTs.[15,20,21] However, these studies included too few non-seminomatous RP or CNS primary to make a meaningful comparison to our cohort. Larger studies, on the other hand, showed that 88% of
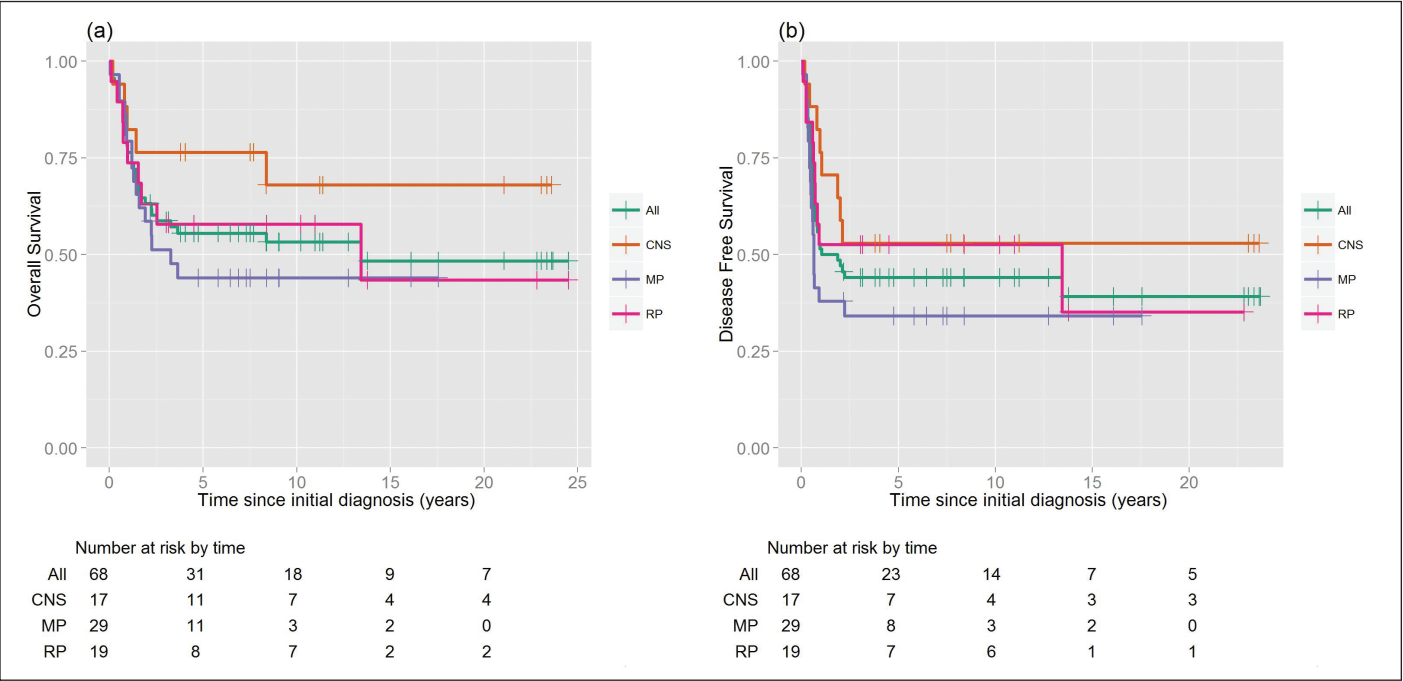


**Fig. 2.** Kaplan-Meier curve of the overall survival **(a)** and disease-free survival **(b)**, for the overall cohort and subgroups by primary site; X-axis in months; All: all patients with EGCT; CNS: intracranial primary GCT; MP: mediastinal primary GCT; RP: retroperitoneal primary GCT.

seminomatous EGCTs, but only 45% of non-seminomatous EGCTs, achieved long-term DFS.[11,17] Furthermore, patients with non-seminomatous RPs had survival just as poor as those with MPs, an intriguing finding given that there exists evidence that RPs may simply represent GGCTs with burnt-out gonadal primary.[22,23] Inferior survival in EGCTs may be in part due to relative insensitivity to cisplatin-based chemotherapy and aggressive pathology inherent in EGCTs. For example, Pectasides et al showed that non-seminomatous EGCTs had a greater degree of p53, MIB-1, and COX-2 overexpression compared with matched cohorts of GGCTs and seminomatous EGCTs, demonstrating potential biologic differences.[24] Recent large trials, such as EORTC 30983 and GETUG 13, reported improved DFS, but similar OS with more intensive chemotherapy regimens in patients with high-risk GGCT.[25,26] More studies are needed to elucidate whether more intensive chemotherapy or targeted therapy can improve outcomes in patients with EGCTs.

Salvage therapy in our patients with relapsed disease, especially of RPs, also did not seem as effective as that reported in GGCT. In literature, about 19% of patients with recurrent EGCT achieve long-term DFS (11% mediastinal, 30% retroperitoneal).[27] Our study included a high proportion of non-seminoma, especially in the retroperitoneal group, with less frequent use of high-dose chemotherapy with stem cell support. In our cohort, TIP was most frequently used for salvage chemotherapy, while VIP (etoposide, ifosfamide and cisplatin) or VeIP regimens are commonly used in other centres, both as upfront and salvage therapy.[27,28] Also, none of our patients with RPs received high-dose chemotherapy with stem cell support after first relapse, perhaps due to a perception that salvage chemotherapy may be sufficient for relapse. However, most of our patients who had salvage surgery had viable non-teratomatous malignancy in the surgical pathology. Given these findings, for selected patients with MP- and RP-GCTs who relapse — especially within one year of first-line therapy — aggressive, upfront salvage therapies, such as high-dose chemotherapy with stem cell support, may be appropriate.

Our results confirm the rates of bleomycin lung toxicity in 15–30% of the patients treated with BEP, similar to those reported in GGCT patients (0–46%).[29-31] Importantly, three patients had Grade 3–5 respiratory failure, possibly due to bleomycin exposure, with no clear risk factors otherwise. In our study, almost all patients with MPs and RPs received BEP as first-line therapy. While the BEP regimen is the standard of care in GGCTs and is most established in the management of EGCTs, there is some evidence to suggest that this regimen may interfere with optimal surgical management and postoperative outcomes due to bleomycin-related lung toxicity. For example, in a large case series of surgical resection of residual disease in the EGCT patients, Kesler et al reported that nine of 10 patients who had postoperative mortality and

nine of 26 patients who experienced postoperative complications were attributed to respiratory failure from bleomycin.[32] None of the patients who received chemotherapy regimens other than BEP had respiratory complications. This finding underscores the importance of bleomycin avoidance in patients with potential risk factors for respiratory failure or anticipated surgical resection of residual tumours.

In our cohort with CNS primary, there were seven cases of complete response and long-term survival with first-line chemotherapy alone without RT or surgical resection. CNS GCTs comprise a unique group of GCTs, with no uniform standards of care. In particular, our cohort contained a large proportion of suspected or confirmed non-germinoma. Data on non-germinomatous CNS tumours, including evidence for optimal treatment, are lacking due to their rarity and difficulties in accurate histopathologic diagnosis.[33,34] Generally accepted treatments include radiation therapy with or without chemotherapy, with favourable survival in classic germinoma, but less favourable in mixed histopathology.[35-37] At least one study reports a favourable prognosis and germinoma-like pathology in patients who achieve complete response with chemotherapy, but it is unknown whether a combined modality is superior to a single modality treatment.[38] Even though in vitro studies have shown therapeutic concentrations of bleomycin and etoposide, the penetration of cisplatin into the intracranial space is limited.[39-41] Further studies are needed to clarify the role of first-line radiation and chemotherapy in primary CNS GCTs.

## Conclusion

In summary, EGCT is a rare, but important subset of GCTs. Patients with EGCT, in particular non-seminomatous, have poorer outcomes compared with gonadal primary despite aggressive treatments. Non-seminomatous EGCTs demonstrate relative chemo-resistance and further studies are needed to identify optimal upfront and salvage treatment options.

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