### Treatment and outcomes of UK and German patients with relapsed intracranial germ cell tumors following uniform first-line therapy

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Treatment and outcomes of UK and German patients with relapsed intracranial germ cell tumors following uniform first-line therapy

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Novelty and impact statements

A retrospective assessment of the value of high-dose chemotherapy and autologous stem cell rescue (HDC+AuSCR) and re-irradiation in patients with relapsed intracranial germ cell tumors (GCTs). Those with germinoma had reasonable outcomes with either standard-dose chemotherapy with re-irradiation or HDC+AuSCR; those with relapsed non-germinomatous GCTs (NGGCTs) were only salvaged with HDC+AuSCR, but then only rarely. Counselling regarding poor outcomes for relapsed NGGCT patients is required prior to embarking on treatment.

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Running title: Relapsed intracranial germ cell tumors

Keywords: germ cell tumor; high-dose chemotherapy; intracranial; non-germinoma; relapse, re-irradiation.

Abstract

We aimed to retrospectively assess treatments/outcomes, including the value of high-dose-chemotherapy and autologous-stem-cell-rescue (HDC+AuSCR) and re-irradiation, in a large, European patient-cohort with relapsed intracranial germ-cell-tumors (GCTs) receiving uniform first-line therapy, including radiotherapy as standard-of-care. Fifty-eight UK/German patients (48 male/10 female) with relapsed intracranial-GCTs [13 germinoma/45 non-germinomatous GCT(NGGCT)] treated 1996-2010 as per the SIOP-CNS-GCT-96 protocol were evaluated. For germinoma, six patients relapsed with germinoma and five with NGGCT (one palliative, one teratoma patient excluded). Five-year overall-survival (OS) for the whole-group (n=11) was 55%. Four of six germinoma relapses and two of five relapsing with NGGCT were salvaged; patients were salvaged with either standard-dose-chemotherapy (SDC) and re-irradiation or HDC+AuSCR with/without re-irradiation. Of 45 relapsed NGGCT patients, 13 were excluded (3 non-protocol adherence, 5 teratoma, 5 palliation). Five-year OS for the remaining 32 relapsed malignant NGGCT patients treated with curative intent was 9%(95%CI: 2-26%). By treatment received, 5-year OS for the 10 patients receiving SDC and 22 patients treated with intention for HDC+AuSCR was 0%(0-0%) and 14%(3-36%), respectively. The three relapsed NGGCT survivors had raised HCG markers alone; two received additional irradiation. Patients with relapsed germinoma had better 5-year OS than those with relapsed NGGCT (55%vs.9%; p=0.007). Patients with relapsed germinoma were salvaged both with SDC and re-irradiation or HDC+AuSCR with/without re-irradiation; which both represent valid treatment options. Outcomes for malignant relapse following initial diagnosis of NGGCT were exceptionally poor; the few
survivors received thiotepa-based HDC+AuSCR, which is a treatment option at first malignant relapse for such patients, with further surgery/irradiation where feasible.
Introduction

Malignant intracranial germ cell tumors (GCTs) are a rare group of predominantly midline neoplasms\(^1\), often classified into germinoma or non-germinomatous tumors (NGGCTs). The latter group is particularly heterogeneous and includes the malignant subtypes yolk sac tumor (YST) and choriocarcinoma (CHC) [which secrete the tumor markers alpha-fetoprotein (AFP) and human chorionic gonadotropin (HCG), respectively], as well as embryonal carcinoma (EC)\(^2\). Most NGGCTs are mixed malignant GCTs, containing more than one subtype, which makes diagnostic work-up, classification and management more complex\(^3,4\).

Germinomas comprise ~60% of all intracranial GCTs\(^5\), and are extremely sensitive to multimodal therapy\(^6\), including both chemotherapy and radiotherapy. Recent strategies have focused on maintaining excellent event-free (EFS) and overall (OS) survival rates, whilst reducing toxicity and late-effects\(^5,7-9\). The European non-randomized trial, SIOP-CNS-GCT-96, compared craniospinal radiotherapy (CSI) alone (24 Gy plus 16 Gy tumor-boost), Option-A, with two courses of combination ‘carboPEI’ chemotherapy (carboplatin/etoposide/ifosfamide) and focal radiotherapy (40 Gy), Option-B, for localized intracranial germinomas\(^5\). Metastatic disease was treated with either CSI alone or combination chemotherapy (as for localized disease) and CSI. Outcomes were excellent, with five-year EFS of 94% and 88% for localized patients treated with Options-A and -B, respectively\(^5\). An excess of ventricular relapses for Option-B patients was addressed by the addition of whole ventricular irradiation for the current SIOP-CNS-GCT-II study\(^5\). In germinoma patients with metastatic disease, five-year EFS and OS was 98%\(^5\).
Patients with NGGCT on the SIOP-CNS-GCT-96 study received four courses of PEI chemotherapy (cisplatin/etoposide/ifosfamide), followed by 54 Gy focal radiotherapy for localized disease and 30 Gy CSI with 24 Gy tumor-boost for metastatic disease. The rationale for treatment was based on studies that used a single chemotherapy protocol to treat both extracranial and intracranial GCT, with the addition of radiation for intracranial cases. Progression-free survival (PFS) was inferior to that observed for germinoma, at 69% and 67% for localized and metastatic disease, respectively. Recently, good outcomes for intracranial NGGCT patients were reported in a Children’s Oncology Group study.

As a consequence of the rarity of intracranial GCTs and the general success of their treatment, relapses are rare. As a result, there is little available evidence to guide optimal management. A widely reported study of relapsed intracranial GCT evaluated the efficacy of HDC+AuSCR in a small, highly heterogeneous group of patients who had received variable first-line treatments. Eight of the 21 patients reported had not received prior radiotherapy, which would now be considered standard-of-care. Furthermore, there was unavoidable selection bias in the patients described, as those who experienced rapid tumor progression or did not have a good response to re-induction chemotherapy did not proceed to HDC+AuSCR and were therefore not reported. As a result, the encouraging outcomes reported (78% and 33% survival for germinoma and NGGCT, respectively) are likely to be an overestimate of the true salvage rates for patients who relapse following optimal first-line treatment. A more recent small study of HDC+AuSCR for relapsed intracranial GCT patients reported promising survival rates, however, first-line treatments were variable.
Here, we present data from the largest cohort of patients with relapsed intracranial GCTs described to date, treated with first-line treatment as per the European SIOP-CNS-GCT-96 trial protocol, which included radiotherapy as standard. The results described here will inform future approaches to the management of these patients, with the aim of optimizing survival.
Patients and Methods

Methods. Both the UK and German groups, as major contributors to the SIOP-CNS-GCT-96 trial, treated sufficient numbers of patients according to the protocol to have a suitable patient cohort experiencing relapse to describe separately. In addition, UK and German groups made resources available to undertake this project. Accordingly, follow-up data on UK and German patients treated on the SIOP-CNS-GCT-96 trial, stored on a central database, was augmented in the UK by additional questionnaire-based data-collection, which captured additional non-trial patients who were treated according to the protocol. This anonymized service evaluation required no additional ethical approvals. Resources were not available to undertake additional questionnaire-based data collection to identify non-trial patients in Germany, or other countries who participated in the trial. Patients included in the study received treatment between 1996 and 2010. The SIOP-CNS-GCT-96 trial was open from 1996 and following closure in the UK in 2006, non-trial patients were treated on trial-based guidelines. Data were collected during 2011, with a further update to exclude further events in 2014. Data requested included full clinico-pathological details at primary diagnosis and relapse, confirmation of first-line treatment, relapse treatments received and outcome. The clinical characteristics of the subset of patients described here were similar to the trial group as a whole.

Overall patient cohort. A total of 58 relapsed central nervous system (CNS) GCT cases were identified from the UK (n=33) and Germany (n=25), comprising 48 male and 10 female patients, with an overall median age at diagnosis of 14.0 years (y) (range 1.4-30.0 y) and median follow-up from original diagnosis of 23 months (m)
There were 13 cases with an original diagnosis of germinoma (10 UK/three German; nine male/four female) and 45 patients who relapsed following an NGGCT diagnosis (23 UK/22 German; 39 male/six female). Of the 58 patients identified in total, 41 (71%) were treated on trial (16 UK and 25 German patients). The trial database only captured data up until the time of relapse, and therefore subsequent information regarding treatments and outcome available on the database was variable. Consequently, further anonymized information was sought from treating centers. An additional 17 (29%) UK non-trial patients were identified by questionnaire-based survey, hence the relative larger number of UK relapses. For germinoma, the 10 UK patients comprised five trial and five non-trial patients (in addition to the three German trial patients). For the 23 UK NGGCT cases, 11 patients were treated on trial with a further 12 non-trial patients identified (in addition to the 22 German trial patients). From the trial database, overall outcomes for UK and German patients receiving first-line treatment were similar to overall trial results for patients from all participating countries (data not shown), and hence represented an appropriate and non-biased cohort in which to study relapse. It should be noted that the purpose of this work was not to assess the actual relapse rate for CNS GCTs and, indeed, as both trial and non-trial patients were included, it was not possible to provide an overall denominator defining the total number of patients treated upfront, which are provided elsewhere. See Figure 1 for a summary flow-diagram of patients included in the study.

Relapsed germinoma patients – initial diagnostic and staging work-up. Clinico-pathological data at diagnosis are summarized in Supplementary Table 1. The median age at diagnosis of the 13 patients who relapsed following a germinoma diagnosis was
12.3 y (range 4.8-16.3 y). Primary disease site was pineal gland (n=5), suprasellar region (n=4), bifocal (i.e. suprasellar and pineal regions, considered localized disease if no evidence of disease elsewhere; n=3) and basal ganglia (n=1). All cases underwent histological confirmation of germinoma diagnosis. One of 13 cases (8%) was metastatic at diagnosis.

**Relapsed germinoma patients – first-line treatment received and response.** Data are summarized in Supplementary Table 1. Seven of 13 patients (54%) received CSI as per Option-A treatment on the SIOP-CNS-GCT-96 protocol, and 6/13 (46%) patients received Option-B treatment with combined chemotherapy and focal radiotherapy. In the absence of central radiological review to assess response in the SIOP-CNS-GCT-96 trial, local radiological reports were utilized for both trial and non-trial patients in this study. Eight of 13 patients (62%) achieved a complete response (CR) to first-line therapy, 4/13 achieved a partial response (PR; 31%) and data were unavailable for one patient (8%).

**Relapsed NGGCT patients – initial diagnostic and staging work-up.** Clinico-pathological data are summarized in Supplementary Table 2. The median age at diagnosis of the 45 patients who relapsed following an NGGCT diagnosis was 14.4 y (range 1.4-30.0 y). Primary disease site was pineal (n=27), suprasellar (n=8), bifocal (n=4), basal ganglia (n=3) and cerebral hemisphere (n=3). Forty-one of 45 cases (91%) had markers above SIOP-CNS-GCT-96 defined thresholds (i.e. serum or CSF AFP >25 ng/ml and/or HCG >50 IU/l) and the remaining four cases had negative markers, so underwent a neurosurgical biopsy which histologically confirmed EC. Six
of 45 cases (13%) were metastatic at diagnosis, defined by imaging and/or CSF cytology.

Relapsed NGGCT patients – first-line treatment received and response. Data are summarized in Supplementary Table 2. Forty-two of 45 patients (93%) received standard PEI chemotherapy, and three (7%) received non-protocol chemotherapy and were excluded from subsequent relapse outcome analysis: one received ‘high-dose’ PEI due to presentation after trial closure with AFP ≥1000 ng/ml, as per the SIOP-CNS-GCT-II trial treatment prior to its opening (physician choice), and two received other chemotherapy (no indication given). Forty-three of 45 patients (96%) received radiotherapy, one had progressive disease prior to receiving radiotherapy and the other was considered too young (19m) at diagnosis. As per standard criteria\textsuperscript{16}, 14 of 45 patients (31%) achieved CR at the end of first-line treatment, 20/45 (44%) achieved partial remission (PR), 6/45 (13%) had stable disease (SD), 4/45 (9%) had progressive disease (PD) and data were unavailable for one patient (2%). Five of the 26 patients (19%) with a PR/SD response underwent surgical resection for residual disease.

Statistical analysis. EFS was calculated from day of relapse to date of progression or death, whichever was earlier, with censoring taken on the date of last clinical contact. OS was calculated from date of relapse to date of death. Estimated EFS/OS rates were calculated by Kaplan-Meier survival method. EFS/OS values were given with 95% confidence intervals (CI) in parentheses, and differences in outcome between groups assessed by log-rank test ($p \leq 0.05$ significant), where numbers were sufficient for such statistical analyses/comparisons.
Results

Relapsed patients – details of relapse. Data are summarized in Figure 1, Table 1, Table 2 and Supplementary Results.

Relapsed germinoma patients – relapse treatments and outcomes. Data are summarized in Figure 1 and Table 1. Two patients (both treated initially on Option-A) were excluded from further evaluation – one was a pure immature teratoma relapse and one declined active treatment. The majority of the 11 remaining patients who had a malignant relapse treated with curative intent following original germinoma diagnosis received re-induction chemotherapy with a platinum-based (carboplatin or cisplatin) strategy (Table 1), with variable subsequent treatments. This resulted in a 5-year EFS and OS of 5/11 (45%) and 6/11 (55%), respectively, with median EFS and OS of 20 m and 53 m for the whole group, respectively (Figure 2). Median OS for the six survivors was 84 m (range 53-194 m). We first compared OS by original first-line treatment, irrespective of subsequent relapse chemotherapy delivered. Of the five patients treated on Option-A, two survived (40%), with four of six surviving (67%) who initially received Option-B (Supplementary Table 1 and Table 1). Next, we compared the cohort by relapse chemotherapy/re-irradiation received. Three out of seven patients (43%) treated with standard-dose-chemotherapy (SDC) had complete responses and no further relapses/events; the figure was 2/4 (50%) who received HDC+AuSCR at first relapse. Two patients received HDC+AuSCR following further relapse after SDC, of whom one was salvaged, taking the OS of patients treated with SDC at initial relapse to 4/7 (57%) (Table 1). Six out of seven patients (86%) treated with SDC received additional radiotherapy (four focal, plus two patients who had CSI having received focal radiotherapy at original diagnosis). One SDC patient, who had
CSI at diagnosis, received no further radiotherapy at relapse. None of the four patients who were treated with intent for HDC+AuSCR received additional radiotherapy at relapse. Finally, we compared the group by presence or absence of positive tumor markers at relapse. For marker-negative (i.e. germinoma) cases at relapse, 5-year EFS and OS was 3/6 (50%) and 4/6 (67%), respectively. Three of these six patients were treated with SDC (in addition to focal re-irradiation), of whom two (67%) were salvaged – one with SDC alone and the other with additional HDC+AuSCR following a second relapse. Three of the six patients were treated with HDC+AuSCR at first relapse, with no further re-irradiation, of whom two (67%) were salvaged. Of the five patients who relapsed and were marker-positive (i.e. classified as NGGCT at relapse), two patients of four (50%) were successfully treated with SDC alone (Table 1). Of these two survivors, one had a CNS relapse (treated with SDC and CSI) with a maximum HCG level of only 55 IU/l (patient G12); the other had an exclusively extracranial relapse due to tumor seeding through a ventriculo-peritoneal shunt, with only germinoma confirmed on cytology of ascitic fluid and an HCG of 397 IU/l (G13), described elsewhere\textsuperscript{17}. The other germinoma patient who relapsed with positive HCG (patient G2; maximum HCG value 734 IU/l), received SDC, but subsequently died following further relapses after having received HDC+AuSCR. One germinoma patient relapsing as NGGCT received HDC+AuSCR at first relapse, who also subsequently died (Table 1).

Relapsed NGGCT patients - relapse treatment and outcomes. Data are summarized in Figure 1 and Table 2. Of the 45 relapsed NGGCT patients, 13 were excluded, comprising non-protocol first-line chemotherapy (n=3), relapse with pure teratoma, treated with surgery alone (n=5), and a further five patients who received palliation...
only (see Figure 1). As for relapsed germinoma, the majority of relapsed NGGCT patients treated with curative intent received re-induction chemotherapy with a platinum-based (carboplatin or cisplatin) strategy, with most of those patients then proceeding to high-dose therapy (Table 1). Five-year EFS and OS for these 32 remaining malignant patients treated with curative intent was 9% (95% CI: 2-26%), with a median EFS and OS of 8m and 12m, respectively (Figure 2). Median OS for the three survivors was 105 m (range 88-127 m). Five-year OS for the 10 patients who received SDC was 0% (0-0%), with median survival of 9 m; all died 3-43 m following relapse (Figure 3). Of these 10 patients, four (40%) received CSI at first relapse, two (20%) received focal re-irradiation and four (40%) received no further radiotherapy. Five-year OS for the 22 patients treated with intention for HDC+AuSCR was 14% (3-36%) with median survival of 12 m; only three patients survived and the others all died 3-35 m following relapse (Figure 3). Of these 22 patients, five (23%) received focal re-irradiation at first relapse, eight (36%) received CSI and nine (41%) received no further irradiation. Data analysis was performed on the basis of physician intention to treat, but 6/22 patients (27%) did not receive HDC+AuSCR because either they experienced further disease progression and died before initiation of HDC, or because they were too clinically unwell to receive it. Of the 16 patients who actually received HDC+AuSCR, 13 died (range 3-35 m), one is alive with SD (at 88 m follow-up) and two patients are in CR (at 105 m and 127 m). It is of note that the two CR patients both received additional radiation.

**Associations with survival in relapsed CNS GCTs.** Clinico-pathological factors were interrogated for potential associations with clinical outcome. Firstly, patients who relapsed following an original diagnosis of germinoma (n=11) had better 5-year EFS
and OS than those who relapsed following an original diagnosis of NGGCT (n=32) 
(p=0.01 and p=0.007, respectively) (Figure 2). In the latter group, the only three 
survivors were all noted to have raised serum/CSF HCG levels alone (defined as HCG 
>50 IU/l at either diagnosis or relapse). Comparing the NGGCT relapse group treated 
with curative intent (n=32), regardless of relapse treatment received (intention for 
HDC+AuSCR or SDC), this ‘raised HCG alone’ group (n=7) had significantly better 
5-year OS (3/7; 43%) than all other relapsed NGGCT patients (0/25; 0%), (p=0.003) 
(Figure 4A). To avoid potential confounding by relapse treatment received, we next 
repeated this HCG analysis for only the 22 relapsed NGGCT patients with intention to 
treat with HDC+AuSCR. This also demonstrated a significantly better 5-year OS 
(p=0.002) for the four patients with raised HCG alone (3/4 survivors; 75%) compared 
with all other patients in the HDC+AuSCR cohort (0/18 survivors; 0%) (Figure 4B). 
Within the ‘raised HCG alone’ group, there were, however, no significant differences 
in the maximum levels of HCG between the patients who survived (n=3; levels 113, 
4,664, 5,999 IU/L) and those who died (n=4; levels 608, 3,201, 3,559, 60,600 IU/L) 
(p=0.49). For other associations with clinical factors, see Supplementary Results.
Discussion

Intracranial germ cell tumors (GCTs) are a rare, heterogeneous cancer group and first-line treatments are generally successful, so relapse is rare\textsuperscript{2,3,7}. Previous reports describing outcomes of patients with relapsed intracranial GCTs are therefore limited by either small sample size\textsuperscript{14,18-22}, selection bias and/or variable first-line treatments\textsuperscript{14,15,21,23}. For example, eight of 21 patients described in one study\textsuperscript{14} and six of 20 patients in another\textsuperscript{15} evaluating HDC+AuSCR for relapsed intracranial GCTs had not received first-line radiotherapy, which would now be considered standard-of-care for both intracranial germinoma and NGGCT patients\textsuperscript{2,4,22,24}. Consequently, treatments for relapsed disease remain varied with no consensus on optimal management\textsuperscript{2}. To address these limitations, we collected data from UK and German patients with relapsed intracranial GCTs, treated with standardized, first-line treatment as per the European SIOP-CNS-GCT-96 trial protocol. This has allowed us to describe the treatment received and subsequent outcome of the largest cohort of patients with relapsed intracranial GCTs to date. Appropriately, patients with non-uniform first-line treatment, those relapsing with teratoma only and those treated palliatively at relapse were excluded from further outcome analysis. The results will inform future approaches to the management of this disease, with the aim of maximizing survival.

Given the excellent EFS for patients with intracranial germinoma\textsuperscript{5,25,26}, relapses were a very rare occurrence indeed – indeed we only identified a total of 13 such cases across two large national groups (UK/Germany) contributing to the European SIOP-CNS-GCT-96 study. Consequently, this germinoma cohort represents a relatively
small and heterogeneous group, in terms of type of relapse (marker-negative vs. marker-positive) and relapse treatments delivered (SDC vs. HDC+AuSCR; re-irradiation vs. none). Full details are provided in Supplementary Discussion. Outcomes for patients who relapsed following germinoma diagnosis were broadly similar, whether treated with SDC or HDC+AuSCR. It should also be emphasised that whilst no patient in this group receiving HDC+AuSCR had additional radiotherapy, all such patients who received SDC had further radiotherapy (focal or CSI), except for a single patient with extracranial relapse (patient G13). Re-irradiation is therefore likely to make an important contribution to the similar outcomes observed between the two chemotherapy groups. These data therefore support either treatment option for these patients.

As expected, due to the inferior outcomes for patients with intracranial NGGCTs compared with germinoma\textsuperscript{12,26}, relapses amongst this cohort were more common, with 45 cases identified. Of the 32 cases with uniform first-line therapy and malignant relapse treated with curative intent, outcomes were very poor. There were no survivors in the patient group treated with SDC, and long-term OS was only 14% for the group with physician intention-to-treat with HDC+AuSCR. Indeed, over a quarter of this latter cohort did not actually receive HDC+AuSCR as they either progressed during re-induction chemotherapy or were too unwell to receive it. The outcomes described here are inferior to survival rates reported in previous studies: the 33% four-year survival rate described in a cohort of 12 patients\textsuperscript{14} and 59% three-year survival in a cohort of eleven patients\textsuperscript{15} with relapsed NGGCTs who received HDC+AuSCR following variable first-line therapy. It should be noted that if only those patients who actually went on to receive HDC+AuSCR with a thiotepa-based regimen are
considered, survival was 30% (three of 10 patients; Table 2) – similar to that previously described\textsuperscript{14}. However, the overall inferior outcomes described here are more likely to be representative of this patient cohort as a whole. This is due to our study ensuring that outcome analyses were only performed on patients receiving uniform first-line treatment, and inclusion of cases from the time-of-relapse on a curative intention-to-treat basis, and not just those who responded well enough to proceed to HDC+AuSCR. Accordingly, patients need to be counselled regarding these poor outcomes at the time of relapse.

Of note, the only three survivors within the NGGCT relapse group had raised HCG alone, either at original diagnosis or at relapse. All other patients, i.e. those with raised AFP, combined raised AFP and HCG, or those who were marker-negative but had EC confirmed on biopsy, all died following relapse, regardless of salvage therapy delivered. Furthermore, at relapse, those patients with raised HCG alone had improved OS, both for the group as a whole, and when just those patients with intention-to-treat with HDC+AuSCR were considered, where three of four patients with raised HCG were long-term survivors. Survival did not appear to be related to the actual HCG level however, because one of the three surviving patients had a maximum HCG level of 113 IU/L and the other two had levels $>4,500$ IU/L. Although the first patient had a level again potentially consistent with HCG production from syncytiotrophoblast within a pure germinoma, the other two patients had levels that all national groups would consider to represent the presence of CHC within the tumor. These observations do highlight, however, the importance of attempting to agree an internationally agreed cut-off/threshold for tumor-markers, in order to better understand the correlation between marker levels, histology and...
clinical outcome. Such agreement will facilitate trials to improve survival rates for patients with NGGCT whilst avoiding unnecessary treatment for those with germinoma. HDC+AuSCR is therefore a treatment option for patients diagnosed initially with NGGCT and experiencing a malignant relapse, if curative intent is the aim. Additional surgery and/or radiotherapy should also be delivered where feasible – it should be noted that of the three survivors, the two who had CR both received re-irradiation. For commentary on EC subtype relapses, see Supplementary Discussion.

Recent advances in our biological understanding are likely to assist clinical management decisions in the future, through improved risk stratification systems and the identification of molecular targets that will help determine the selection of appropriate novel therapeutic agents, particularly for the NGGCT patient population that have inferior outcomes. Recent use of exome sequencing to identify common genomic mutations is one such example. Collection of serum/plasma and CSF may also facilitate non-invasive diagnosis using microRNA expression levels and risk stratification through identification of tumor mutations via CSF tumor DNA (ctDNA) analysis. Embedding such non-invasive biological studies in future clinical trials is a particularly attractive strategy for trial groups where NGGCT tissue specimens are a scarce resource due to reliance on typical radiology and tumor markers for diagnosis.

The main limitation of this study, as in previous reports, is its retrospective nature. However, as relapse is a rare outcome of this infrequent malignancy, a prospective randomised trial of relapsed CNS GCT patients is unlikely to be feasible. In future, it will be important to ensure that prospective data collection is embedded routinely.
within treatment guidelines, to facilitate the identification of optimal re-induction strategies and further assess the role of HDC in this setting.

In conclusion, we present the largest cohort of patients with relapsed intracranial GCTs reported to date. This study benefits from the uniform manner in which patients received first-line treatment, including radiotherapy as standard-of-care. Patients with an original diagnosis of intracranial germinoma experiencing relapse were salvageable with SDC and re-irradiation and HDC+AuSCR with and without re-irradiation. Patients relapsing following an original diagnosis of intracranial NGGCT fared very poorly; only patients with raised HCG levels alone survived in this series, and only then with HDC+AuSCR. Thiotepa-based HDC+AuSCR, with additional surgery and radiotherapy where feasible, is a treatment option at first malignant relapse for such patients, albeit with counselling regarding poor outcomes.
References


15. Baek HJ, Park HJ, Sung KW, et al. Myeloablative chemotherapy and autologous stem cell transplantation in patients with relapsed or progressed...


22. Baranzelli MC, Patte C, Bouffet E, et al. An attempt to treat pediatric...


Legends to Figures and Tables

Figure 1. Summary flow-diagram listing the 58 patients described in the study and their basic clinical characteristics.

Figure 2. Kaplan-Meier curves comparing five-year A) event-free survival and B) overall survival for patients treated with curative intent: intracranial malignant relapse of germinoma (solid line) versus non-germinomatous germ-cell-tumor (NGGCT; broken line).

Figure 3. Kaplan-Meier curves comparing five-year overall survival for patients treated with curative intent at first malignant relapse of intracranial non-germinomatous germ-cell-tumor (NGGCT): intention for high-dose chemotherapy (solid line) versus those receiving standard-dose chemotherapy (broken line). N/S = non-significant.

Figure 4. Kaplan-Meier curves comparing five-year overall survival for patients treated with curative intent at first malignant relapse of intracranial non-germinomatous germ-cell-tumor (NGGCT) with: elevated levels of HCG alone (solid line) versus all other patients in the cohort* (broken line). Graphs show data for A) all 32 patients regardless of malignant relapse treatment schedule and B) the 22 patients treated with intention for high-dose chemotherapy only. *i.e., all those patients with elevated levels of AFP, combined elevations of AFP/HCG and/or with a tissue diagnosis of EC either in the serum or CSF, at diagnosis and/or relapse.
Table 1. Details of the intracranial germinoma patients at relapse, description of relapse treatments received and outcomes.

Table 2. Details of the intracranial non-germinomatous germ-cell-tumor (NGGCT) patients at relapse, description of relapse treatments received and outcomes.
Figure 1. Summary flow-diagram listing the 58 patients described in the study and their basic clinical characteristics.

Relapse patients identified
(n=58)

Initial diagnosis -
Germinoma
(n=13)

Exclusions (n=2):
Teratoma (n=1)
Palliative (n=1)

Malignant relapse treated
with curative intent
(n=11)

Treatment received at
first relapse

Standard-dose
chemotherapy
(n=7)

Dead (n=3)
Alive (n=4)

High-dose
chemotherapy
(n=4)

Dead (n=2)
Alive (n=2)

Initial diagnosis -
Non-germinomatous
germ cell tumor (n=45)

Exclusions (n=13):
Treatment non-
adherence (n=3)
Teratoma (n=5)
Palliative (n=5)

Malignant relapse treated
with curative intent
(n=32)

Treatment received at
first relapse

Standard-dose
chemotherapy
(n=10)

Dead (n=10)
Alive (n=0)

Intention for high-dose
chemotherapy
(n=22)

Dead (n=19)
Alive (n=3)
Figure 2. Kaplan-Meier curves comparing five-year A) event-free survival and B) overall survival for patients treated with curative intent: intracranial malignant relapse of germinoma (solid line) versus non-germinomatous germ cell tumor (NGGCT; broken line).
Figure 3. Kaplan-Meier curves comparing five-year overall survival for patients treated with curative intent at first malignant relapse of intracranial non-germinomatous germ cell tumor (NGGCT): intention for high-dose chemotherapy (solid line) versus those receiving standard-dose chemotherapy (broken line). N/S = non-significant.
Figure 4. Kaplan-Meier curves comparing five-year overall survival for patients treated with curative intent at first malignant relapse of intracranial non-germinomatous germ cell tumor (NGGCT) with: elevated levels of HCG alone (solid line) versus all other patients in the cohort (broken line). Graphs show data for A) all 32 patients regardless of malignant relapse treatment schedule and B) the 22 patients treated with intention for high-dose chemotherapy only.

A

- 'Raised HCG alone' relapse (n=7)
- Other NGGCT relapse (n=25)

log-rank test $p = 0.003$

Months from time of relapse

Overall survival (%)

B

- 'Raised HCG alone' relapse (n=4)
- Other NGGCT relapse (n=18)

log-rank test $p = 0.002$

Months from time of relapse
Table 1. Details of the intracranial germinoma patients at relapse, description of relapse treatments received and outcomes.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Site(s) of disease at relapse</th>
<th>Elevated tumor markers identified at relapse?</th>
<th>Diagnosis at relapse</th>
<th>Surgery for relapse?</th>
<th>HDC or SDC?</th>
<th>Chemotherapy received</th>
<th>Radiotherapy received</th>
<th>Response</th>
<th>Morbidity described?</th>
<th>Further relapses?</th>
<th>Outcome</th>
<th>Time (from relapse) of death or latest follow up (months)</th>
<th>Included in further analysis?</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Ventricular</td>
<td>No</td>
<td>Presumed germinoma</td>
<td>No</td>
<td>SDC</td>
<td>Re-induction (carboPEI)</td>
<td>Focal CR</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>DOC (sepsis, brainstem impairment)</td>
<td>16</td>
<td>Yes</td>
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<tr>
<td>G4</td>
<td>Distant intracranial</td>
<td>No</td>
<td>Immature teratoma (histology)</td>
<td>Total resection</td>
<td>SDC</td>
<td>Re-induction (carboPEI)</td>
<td>No CR</td>
<td>Metabolic imbalance</td>
<td>3 (treatment included HDC)</td>
<td>DOD</td>
<td>No (immature teratoma)</td>
<td>10</td>
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<tr>
<td>G5</td>
<td>Primary</td>
<td>No</td>
<td>Germinoma (histology)</td>
<td>Total resection</td>
<td>HDC</td>
<td>Re-induction (PEI); HDC (carbo/etop)</td>
<td>No CR</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>AND</td>
<td>194</td>
<td>Yes</td>
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<td>G7</td>
<td>Primary</td>
<td>No</td>
<td>Presumed germinoma</td>
<td>No</td>
<td>HDC</td>
<td>Re-induction (carboPEI); HDC (thiotepa/etop)</td>
<td>None CR</td>
<td>Infection</td>
<td>None</td>
<td>None</td>
<td>DOC (pneumonitis)</td>
<td>5</td>
<td>Yes</td>
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<td>G8</td>
<td>Ventricular</td>
<td>No</td>
<td>Presumed germinoma</td>
<td>No</td>
<td>SDC</td>
<td>Re-induction (PEI)</td>
<td>Focal CR</td>
<td>None</td>
<td>1 (treatment included HDC)</td>
<td>AND</td>
<td>92</td>
<td>Yes</td>
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<tr>
<td>G9</td>
<td>Distant intracranial</td>
<td>No</td>
<td>Presumed germinoma</td>
<td>No</td>
<td>N/A</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>N/A</td>
<td>N/A</td>
<td>DOD</td>
<td>0</td>
<td>No (palliative)</td>
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<td>G10</td>
<td>Extracranial (skeletal)</td>
<td>No</td>
<td>Germinoma (histology)</td>
<td>Biopsy</td>
<td>HDC</td>
<td>Re-induction (PEI); HDC (thiotepa/etop)</td>
<td>None CR</td>
<td>Paanhypopituitarism</td>
<td>None</td>
<td>AND</td>
<td>53</td>
<td>Yes</td>
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<td>G11</td>
<td>Distant intracranial</td>
<td>No</td>
<td>Germinoma (histology)</td>
<td>Partial resection</td>
<td>SDC</td>
<td>Re-induction (other)</td>
<td>Focal CR</td>
<td>Paanhypopituitarism</td>
<td>None</td>
<td>AND</td>
<td>148</td>
<td>Yes</td>
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<td>G2</td>
<td>Leptomeningeal</td>
<td>HCG</td>
<td>CHC (markers)</td>
<td>No</td>
<td>SDC</td>
<td>Re-induction (other)</td>
<td>CSI CR</td>
<td>Electrolyte imbalance, seizures</td>
<td>2 (treatment included HDC)</td>
<td>DOD</td>
<td>47</td>
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<td></td>
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<td>G3</td>
<td>Primary</td>
<td>AFP</td>
<td>YST (markers)</td>
<td>No</td>
<td>HDC</td>
<td>Re-induction (PEI); HDC (not specified)</td>
<td>No PD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>DOD</td>
<td>8</td>
<td>Yes</td>
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<td>G6</td>
<td>Primary</td>
<td>AFP</td>
<td>Germinoma (histology); YST (markers)</td>
<td>Total resection</td>
<td>SDC</td>
<td>Re-induction (PEI)</td>
<td>Focal PD</td>
<td>None</td>
<td>None</td>
<td>1 (treatment not specified)</td>
<td>DOD</td>
<td>8</td>
<td>Yes</td>
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<td>G12</td>
<td>Ventricular and leptomeningeal</td>
<td>HCG</td>
<td>CHC (markers)</td>
<td>No</td>
<td>SDC</td>
<td>Re-induction (PEI)</td>
<td>CSI CR</td>
<td>DI</td>
<td>None</td>
<td>None</td>
<td>AND</td>
<td>62</td>
<td>Yes</td>
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<tr>
<td>G13</td>
<td>Extracranial (abdominal via VPS)</td>
<td>HCG</td>
<td>Germinoma (cytology of ascites but CHC (markers)</td>
<td>Total resection of residual after chemotherapy</td>
<td>SDC</td>
<td>Re-induction (JEB)</td>
<td>No CR</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>AND</td>
<td>75</td>
<td>Yes</td>
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Abbreviations:
SDC = standard-dose chemotherapy, HDC = high-dose chemotherapy
CHC = choriocarcinoma
YST = yolk sac tumor
MGCT = malignant germ cell tumor
CarboPEI = carboplatin, etoposide, ifosfamide
PEI = cisplatin, etoposide, ifosfamide
carbo/etop = carboplatin, etoposide
thiopeta/etop = thiopeta, etoposide
JEB = carboplatin, etoposide, bleomycin
CSI = craniospinal irradiation
CR = complete response, PR = partial response, PD = progressive disease
AFP = alpha-fetoprotein; defined as elevated in serum or cerebrospinal fluid when levels >25 ng/ml
HCG = human chorionic gonadotrophin, defined as elevated in serum or cerebrospinal fluid when levels >50 IU/l
DOD = died of disease, DOC = died of complication, AND = alive with no disease
N/A = not applicable
DI = diabetes insipidus
VPS = ventriculo-peritoneal shunt
Table 2: Details of the intracranial non-germinomatous germ-cell-tumor (NGGCT) patients at relapse, description of relapse treatments received and outcomes.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Site(s) of disease at relapse</th>
<th>Elevated AFP serum or CSF levels identified at relapse?</th>
<th>Elevated HCG serum or CSF levels identified at relapse?</th>
<th>Diagnosis and additional histological confirmation</th>
<th>Surgery for relapse?</th>
<th>Intention to treat with HDC + AuSCR</th>
<th>Received HDC?</th>
<th>Chemotherapy received</th>
<th>Subsequent radiotherapy</th>
<th>Response</th>
<th>Morbidity</th>
<th>Number of further relapses and treatment received</th>
<th>Outcome</th>
<th>Time of death from 1st relapse (months)</th>
<th>Included in analysis?</th>
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<tbody>
<tr>
<td>NG1</td>
<td>Distant intracranial</td>
<td>+</td>
<td>-</td>
<td>YST (markers)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Re-induction (carbo/PEI); HDC not received – disease progression</td>
<td>Focal</td>
<td>PD</td>
<td>Neurological (seizures)</td>
<td>N/A</td>
<td>DOD 13</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>NG2</td>
<td>Primary</td>
<td>+</td>
<td>-</td>
<td>YST (markers)</td>
<td>Subtotal resection</td>
<td>Yes</td>
<td>Yes</td>
<td>Re-induction (carbo/PEI); HDC (thiotepa-based)</td>
<td>Focal</td>
<td>PR</td>
<td>Toxicity from chemotherapy (not specified)</td>
<td>None</td>
<td>DOD 7</td>
<td>Yes</td>
<td></td>
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<tr>
<td>NG3</td>
<td>Distant intracranial</td>
<td>-</td>
<td>++</td>
<td>CHC (markers)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Re-induction (carbo/PEI); HDC (etop)</td>
<td>None</td>
<td>CR</td>
<td>None</td>
<td>1 (HDC)</td>
<td>DOD 18</td>
<td>Yes</td>
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<tr>
<td>NG4</td>
<td>Not specified</td>
<td>-</td>
<td>-</td>
<td>Teratoma (histology), YST (markers)</td>
<td>Subtotal resection</td>
<td>N/A</td>
<td>N/A</td>
<td>None</td>
<td>None</td>
<td>PR</td>
<td>None</td>
<td>1 (surgery)</td>
<td>DOD 30</td>
<td>No (teratoma)</td>
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<td>NG5</td>
<td>Primary, ventricular, spinal</td>
<td>+</td>
<td>-</td>
<td>Germinoma (histology), YST (markers)</td>
<td>Subtotal resection</td>
<td>Yes</td>
<td>Yes</td>
<td>Not specified</td>
<td>None</td>
<td>PD</td>
<td>None</td>
<td>None</td>
<td>DOD 6</td>
<td>Yes</td>
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<tr>
<td>NG6</td>
<td>Primary</td>
<td>-</td>
<td>-</td>
<td>Teratoma (histology)</td>
<td>Total resection</td>
<td>N/A</td>
<td>N/A</td>
<td>None</td>
<td>None</td>
<td>CR</td>
<td>None</td>
<td>None</td>
<td>AND 65</td>
<td>No (teratoma)</td>
<td></td>
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<tr>
<td>NG7</td>
<td>Primary</td>
<td>-</td>
<td>-</td>
<td>Presumed NGGCT</td>
<td>No</td>
<td>N/A</td>
<td>N/A</td>
<td>None</td>
<td>None</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>DOD 2</td>
<td>No (palliative)</td>
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<tr>
<td>NG8</td>
<td>Primary</td>
<td>-</td>
<td>-</td>
<td>Presumed NGGCT</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Re-induction (not specified); HDC not received – disease progression</td>
<td>None</td>
<td>PD</td>
<td>Infection</td>
<td>N/A</td>
<td>DOD 3</td>
<td>Yes</td>
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<tr>
<td>NG9</td>
<td>Primary</td>
<td>+</td>
<td>-</td>
<td>YST (markers)</td>
<td>No</td>
<td>No</td>
<td>N/A</td>
<td>Re-induction (carbo/etop)</td>
<td>Focal</td>
<td>PD</td>
<td>Infection</td>
<td>None</td>
<td>DOD 19</td>
<td>Yes</td>
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<tr>
<td>NG10</td>
<td>Primary, distant intracranial, spinal</td>
<td>+++</td>
<td>-</td>
<td>YST (markers)</td>
<td>Total resection</td>
<td>Yes</td>
<td>Yes</td>
<td>Re-induction (carbo/etop); HDC (PEI)</td>
<td>CSI</td>
<td>PD</td>
<td>None</td>
<td>1 (not specified)</td>
<td>DOD 6</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>NG11</td>
<td>Primary, spinal</td>
<td>++</td>
<td>-</td>
<td>YST (markers)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Re-induction (carbo/etop); HDC (thiotepa-based)</td>
<td>CSI</td>
<td>PR</td>
<td>Infection</td>
<td>2 (SDC)</td>
<td>DOD 35</td>
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<tr>
<td>NG12</td>
<td>Distant intracranial</td>
<td>-</td>
<td>+</td>
<td>CHC (markers)</td>
<td>No</td>
<td>No</td>
<td>N/A</td>
<td>Re-induction (carbo/etop)</td>
<td>CSI</td>
<td>CR</td>
<td>Neurological (Guillain-Barré syndrome)</td>
<td>1 (palliative)</td>
<td>DOD 12</td>
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<tr>
<td>NG13</td>
<td>Primary, spinal</td>
<td>-</td>
<td>-</td>
<td>Presumed NGGCT</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Re-induction (PEI); HDC not received – disease progression</td>
<td>None</td>
<td>PD</td>
<td>Not specified</td>
<td>N/A</td>
<td>DOD 3</td>
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<td>NG14</td>
<td>Primary</td>
<td>+</td>
<td>-</td>
<td>YST (markers)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Re-induction (carbo/etop); HDC (etop)</td>
<td>None</td>
<td>CR</td>
<td>Infection</td>
<td>1 (SDC)</td>
<td>DOD 14</td>
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<td>NG15</td>
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<td>-</td>
<td>++</td>
<td>CHC (markers)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Re-induction (carbo/PEI); HDC (thiotepa-based)</td>
<td>None</td>
<td>SD</td>
<td>None</td>
<td>None</td>
<td>ASD 88</td>
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<td>NG16</td>
<td>Primary, spinal</td>
<td>-</td>
<td>-</td>
<td>Presumed NGGCT</td>
<td>Metastases resected</td>
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<td>Yes</td>
<td>Re-induction and HDC (HD-PEI)</td>
<td>CSI</td>
<td>CR</td>
<td>Not specified</td>
<td>1 (palliative)</td>
<td>DOD 11</td>
<td>Yes</td>
<td></td>
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</tbody>
</table>

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<p>| NG17 | Primary | F | - | YST (markers) | No | No | N/A | Ventricular etoposide | CSI | SD | None | 1 (palliative) | DOD 8 | Yes |
| NG18 | Primary, spinal | - | - | Germinoma (histology) | No | No | N/A | Re-induction (carbo/etop) | None | PR | Infection, respiratory and renal failure | None | DOD 10 | Yes |
| NG19 | Distant intracranial | Yes (levels not specified) | - | YST (markers) | No | No | N/A | Re-induction (carbo/etop) | CSI | PD | Not specified | 1 (SDC) | DOD 9 | No (non-protocol first-line treatment) |
| NG20 | Primary | - | - | Teratoma (histology) | Total resection | No | N/A | None | None | CR | None | None | AND 79 | No (teratoma) |
| NG21 | Distant intracranial | - | - | Mixed MGCT (histology) | Total resection | No | N/A | None | None | PD | None | 5 (SDC) | DOD 35 | Yes |
| NG22 | Spinal | - | ++ | CHC (markers); EC on initial biopsy | No | No | N/A | Re-induction (etop) | None | PD | Not specified | None | DOD 3 | Yes |
| NG23 | Spinal | +++ | - | YST (markers) | Biopsy Yes | Yes | Re-induction (carbo/cyclophosph); HDC (thiotepa-based) | Focal | PR | None | None | DOD 11 | Yes |
| NG24 | Primary, spinal | + | - | YST (markers) | No | N/A | N/A | Palliative (oral etoposide); Focal (to spine) | PD | Infection, seizures | None | DOD 7 | No (palliative) |
| NG25 | Ventricular | - | - | Presumed germinoma | No | N/A | N/A | None | None | N/A | N/A | None | DOD 0 | No (palliative) |
| NG26 | Distant intracranial | ++ | - | YST (markers) | Total resection | No | N/A | Re-induction (JEB) | Focal | CR | Memory loss | 1 (not specified) | DOD 43 | Yes |
| NG27 | Primary | - | ++ | CHC (markers) | No | Yes | Yes | Re-induction (carbo/etop); HDC (thiotepa-based) | None | CR | DI | 1 (SDC) | DOD 34 | Yes |
| NG28 | Ventricular | - | +++ | CHC (markers) | No | Yes | Yes | Re-induction (carbo/etop); HDC (thiotepa-based) | Focal | CR | Extreme lethargy | None | AND 127 | Yes |
| NG29 | Ventricular, spinal | - | + | CHC (markers) | No | Yes | Yes | Re-induction (pachatixel/etop/cisplatin); HDC (etop/carbo/cyclophos) | None | CR | Hearing loss, mucositis | 1 (palliative) | DOD 17 | Yes |
| NG30 | Primary | + | - | YST (markers) | No | Yes | Yes | Re-induction (carbo/etop); HDC (thiotepa-based) | None | PD | Bone marrow suppression | 1 (HDC) | DOD 11 | Yes |
| NG31 | Primary, spinal | + | - | YST (markers), EC on initial biopsy | No | N/A | N/A | None | CSI | PD | None | None | DOD 1 | No (palliative) |
| NG32 | Spinal | + | - | YST (markers) | No | Yes | No | Re-induction (cisplatin/etop/vinc); HDC not received – disease progression | CSI | PD | None | None | DOD 12 | Yes |
| NG33 | Distant intracranial | ++ | - | YST (markers), EC on initial biopsy | No | No | N/A | Re-induction (carbo/etop) | None | PD | Toxicity from chemotherapy (not specified) | None | DOD 6 | Yes |
| NG34 | Distant | - | - | Presumed | No | Yes | No | Re-induction | CSI | PR | Slow count | None | DOD 9 | Yes |</p>
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<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Location</th>
<th>Tumor</th>
<th>Histology</th>
<th>Initial Biopsy</th>
<th>Treatment</th>
<th>Chemotherapy</th>
<th>Lymphoma</th>
<th>Neuroendocrine</th>
<th>Toxicity</th>
<th>Recovery</th>
<th>Age</th>
<th>Status</th>
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<tbody>
<tr>
<td>NG35</td>
<td>Intracranial, spinal</td>
<td>Ventricle</td>
<td>-</td>
<td>-</td>
<td>Presumed germinoma (non-diagnostic biopsy)</td>
<td>Biopsy</td>
<td>Yes</td>
<td>Yes</td>
<td>Re-induction (carbo/etop); HDC (thiotepa-based)</td>
<td>CR</td>
<td>Mild LD, panhypopituitarism</td>
<td>None</td>
<td>AND</td>
</tr>
<tr>
<td>NG36</td>
<td>Intracranial, spinal</td>
<td>Primary</td>
<td>+++</td>
<td>-</td>
<td>YST (markers)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Re-induction (carbo/etop); HDC (carbo/etop)</td>
<td>Not specified</td>
<td>PD</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>NG37</td>
<td>Intracranial, spinal</td>
<td>Spinal</td>
<td>-</td>
<td>-</td>
<td>CHC (cytology)</td>
<td>No</td>
<td>No</td>
<td>N/A</td>
<td>Re-induction (carbo/etop); then vinblastine/etop</td>
<td>CSI</td>
<td>PD</td>
<td>Tumour caused cord compression</td>
<td>None</td>
</tr>
<tr>
<td>NG38</td>
<td>Intracranial, spinal</td>
<td>Spinal</td>
<td>++</td>
<td>-</td>
<td>YST (markers)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Re-induction (carbo/etop/cyclophos); HDC (thiotepa-based)</td>
<td>CSI</td>
<td>PD</td>
<td>Minimal</td>
<td>1 (HDC)</td>
</tr>
<tr>
<td>NG39</td>
<td>Intracranial, spinal</td>
<td>Primary</td>
<td>-</td>
<td>-</td>
<td>Teratoma (histology)</td>
<td>Partial resection</td>
<td>No</td>
<td>N/A</td>
<td>None</td>
<td>None</td>
<td>PR</td>
<td>Seizures, hemiplegia, LD, panhypopituitarism</td>
<td>None</td>
</tr>
<tr>
<td>NG40</td>
<td>Intracranial, spinal</td>
<td>Primary</td>
<td>+</td>
<td>-</td>
<td>YST (markers)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Re-induction (carbo/etop/cyclophos); HDC (thiotepa-based)</td>
<td>Focal</td>
<td>PR</td>
<td>Intensive care after HDC</td>
<td>1 (palliative)</td>
</tr>
<tr>
<td>NG41</td>
<td>Intracranial, spinal</td>
<td>Spinal</td>
<td>++</td>
<td>-</td>
<td>YST (markers)</td>
<td>Not specified</td>
<td>No</td>
<td>N/A</td>
<td>Re-induction (not specified)</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Leucopenia</td>
<td>None</td>
</tr>
<tr>
<td>NG42</td>
<td>Intracranial, spinal</td>
<td>Leptomeningeal</td>
<td>-</td>
<td>+</td>
<td>CHC (markers)</td>
<td>No</td>
<td>N/A</td>
<td>N/A</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>DOD</td>
</tr>
<tr>
<td>NG43</td>
<td>Intracranial, spinal</td>
<td>Leptomeningeal</td>
<td>+</td>
<td>-</td>
<td>YST (markers)</td>
<td>Total resection</td>
<td>Yes</td>
<td>No</td>
<td>Re-induction (JEB); HDC not received – clinically too unwell</td>
<td>CSI</td>
<td>CR</td>
<td>Candida endocarditis, DI, shunt problems</td>
<td>1 (not specified)</td>
</tr>
<tr>
<td>NG44</td>
<td>Intracranial, spinal</td>
<td>Primary, distant intracranial</td>
<td>-</td>
<td>-</td>
<td>Teratoma (histology)</td>
<td>Total resection</td>
<td>N/A</td>
<td>N/A</td>
<td>None</td>
<td>None</td>
<td>PD</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>NG45</td>
<td>Intracranial, spinal</td>
<td>Leptomeningeal</td>
<td>-</td>
<td>-</td>
<td>Presumed NGCT</td>
<td>None</td>
<td>No</td>
<td>N/A</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>DOD</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- CSI: Chemotherapy, Sterilization, Immuno-suppression
- CR: Complete Remission
- PD: Progressive Disease
- ASD: Age of Survival
- DOD: Date of Death
- JEB: Jethro E. Bell
- HD: High Dose
- LD: Low Dose
- DI: Diaphragm
- DI: Drainage
- NB: Neurologist
- CT: Computerized Tomography
- MRI: Magnetic Resonance Imaging
- F: Fibrous
- H: Haemorrhagic
- S: Sarcomatous
- N/A: Not Applied
- ND: Not Defined
NGGCT = non-germinomatous germ cell tumor
YST = yolk sac tumor
CHC = choriocarcinoma
SDC = standard-dose chemotherapy, HDC = high-dose chemotherapy
CSF = cerebrospinal fluid
AFP = alpha-fetoprotein, defined as elevated in serum or cerebrospinal fluid when levels >25 ng/ml
HCG = human chorionic gonadotrophin, defined as elevated in serum or cerebrospinal fluid when levels >50 IU/l

Marker key:

AFP:
- refers to levels ≤25 ng/ml
+ refers to levels >25 but <200 ng/ml
+++ refers to levels ≥200 but <1000 ng/ml
++++ refers to levels ≥1000 ng/ml

HCG:
- refers to levels ≤50 IU/l
+ refers to levels >50 but <200 IU/l
++ refers to levels ≥200 but <1000 IU/l
+++ refers to levels ≥1000 IU/l

PEI = cisplatin, etoposide, ifosfamide
carbopEI = carboplatin, etoposide, ifosfamide
PEI = cisplatin, etoposide, ifosfamide
carbetoop = carboplatin, etoposide
carbetoop/cyclophos = carboplatin, etoposide, cyclophosphamide
thiotepa/etop = thiotepa, etoposide
cisplatin/etop/vinc = cisplatin, etoposide, vincristine
paclitaxel, etop/cyclophos = paclitaxel, etoposide, carboplatin, cyclophosphamide
JEB = carboplatin, etoposide, bleomycin

CSI = craniospinal irradiation
RT = radiotherapy
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease
DOD = died of disease, DOC = died of complication, ASD = alive with stable disease, AND = alive with no disease
LD = learning difficulties
DI = diabetes insipidus
N/A = not applicable