Outcomes of patients with intracranial germ cell tumour with choriocarcinoma element or β-HCG level higher than 500 IU/L under radiotherapy-based treatments

Jin Feng  
Beijing Tian Tan Hospital  

Li Chen  
Beijing Tian Tan Hospital  

Chunde Li  
Beijing Tian Tan Hospital  

Wei Liu  
Beijing Tian Tan Hospital  

Huiyuan Chen  
Beijing Tian Tan Hospital  

Xiaoguang Qiu  
Beijing Tian Tan Hospital  

Bo Li (libo@bjtth.org)  
Beijing Tian Tan Hospital

Research Article

Keywords: intracranial germ cell tumour, choriocarcinoma, radiotherapy, chemotherapy, beta-human chorionic gonadotropin

Posted Date: December 1st, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2321112/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Background

In previous studies, patients with intracranial germ cell tumour (iGCT) with pure choriocarcinoma or mixed germ cell tumours with choriocarcinoma element showed similar dismal prognoses, with median overall survival (OS) of 22 months and 1-year survival rate of approximately 60%. However, these conclusions need to be updated because radiotherapy, which is the milestone for this disease, was not applied in a number of patients.

Methods

Clinical data of patients with iGCTs with histologically confirmed choriocarcinoma element or beta-human chorionic gonadotropin (β-HCG) > 500 IU/L were collected from the archives of our institution and retrospectively studied.

Results

A total of 76 patients were eligible for this study. In terms of the initial treatment, 11 patients underwent surgery, four patients received radiotherapy, and 61 patients received chemotherapy. Except for two early deaths, all patients received radiotherapy (craniospinal irradiation [CSI], n = 23; non-CSI, n = 51). The median follow-up duration for the entire series was 63 months (range, 6–188 months). The 5-year event-free survival (EFS) and OS rates were 81.5% and 84.1%, respectively. Among patients who did not have early death or progressive disease after induction chemotherapy, multivariate analysis revealed that chemotherapy cycles (> 4 vs. ≤4) (hazard ratio [HR] for EFS 0.144, p = 0.020; HR for OS 0.111, p = 0.028) and β-HCG levels (> 3000 IU/L vs. ≤3000 IU/L) (HR for EFS 4.342, p = 0.059; HR for OS 6.614, p = 0.033) were independent factors for survival. Radiation volume (non-CSI vs. CSI) was not proven to be a prognostic factor for either EFS or OS (hazard ratio [HR] for EFS 1.902, p = 0.59; HR for OS 2.425, p = 0.49).

Conclusions

Patients with iGCTs with choriocarcinoma element or β-HCG > 500 IU/L showed improved survival with radiotherapy-based treatments. Additional chemotherapy cycles could result in additional survival benefits. Patients with β-HCG level > 3000 IU/L had poorer prognosis.

Introduction

Choriocarcinoma is a rare subtype of intracranial germ cell tumours (iGCTs). According to a study conducted by Jiang et al., only 51 patients had pure choriocarcinoma since 1974 [1]. In another study
conducted by Shinoda et al., 66 patients diagnosed with pure choriocarcinoma or mixed germ cell tumours with choriocarcinoma were reported since 1975 [2]. Although the incidence of choriocarcinoma is unknown, it accounts for 3–5% of all iGCTs [3, 4]. Choriocarcinoma is characterised by extremely high serum and cerebrospinal fluid (CSF) levels of beta-human chorionic gonadotropin (β-HCG), which is attributed to both cytotrophoblastic elements and syncytiotrophoblastic giant cells in histology. Spontaneous intratumoral haemorrhage is another characteristic presentation, which may occur at the time of diagnosis or during treatment. It can be life threatening if not dealt with properly. Metastases are common complications, which may occur even beyond the central nervous system. Therefore, choriocarcinoma is considered the most malignant primary iGCT.

To date, several studies have attempted to characterise this fatal disease and explore effective therapeutic strategies. Unfortunately, owing to the rarity of this malignancy, most publications were case reports. Jiang et al. and Shinoda et al. published their studies based on group analyses of data extracted from previous studies [1, 2]. As indicated, both patients with pure choriocarcinoma and mixed germ cell tumours with a choriocarcinoma element had a poor prognosis, with a median overall survival (OS) of 22 months and 1-year survival rate of approximately 60%. The extent of resection was found to correlate with prognosis. The larger the extent of tumour resection, the better the survival of patients. Furthermore, adjuvant radiotherapy and/or chemotherapy have been proven to have additional survival benefits compared with surgery alone. However, among the recruited studies, the treatment strategies were heterogeneous, including surgery alone, radiotherapy alone, chemotherapy alone, or some combinations. Therefore, these conclusions may be limited by inconsistent treatment protocols. Furthermore, given that approximately one-third of patients did not receive radiotherapy, findings regarding the positive role of treatment modalities may be less informative to the current practice since radiotherapy is the milestone for the treatment of iGCTs [5–8].

Thus, to re-evaluate these factors under the current radiotherapy-based treatment pattern, we conducted a retrospective study based on the clinical data of our single institution. Patients with histologically confirmed choriocarcinoma element were eligible for inclusion in the study. Additionally, patients with β-HCG level > 500 IU/L (normal value < 5.0 IU/L) were also recruited.

**Patients And Methods**

**Inclusion criteria**

This retrospective study protocol was reviewed and approved by the institutional review board and ethics committee. The requirement for written informed consent from patients was waived owing to the retrospective study design. The clinical data of 1448 patients with newly diagnosed iGCTs between 2000 and 2019 were screened from the archive of our hospital. Patients with choriocarcinoma element in the histology or serum or CSF β-HCG level > 500 IU/L (normal value < 5.0 IU/L) were eligible for the study.

**Treatment strategy**
At our institution, baseline evaluations included complete blood count, serum chemistry, and radiographic examinations. Craniospinal enhanced-contrast magnetic resonance imaging and serum β-HCG/alpha-fetoprotein (AFP) level measurement were mandatory for all patients. However, CSF testing was reserved primarily for patients with no lumbar puncture contraindications. After baseline evaluation, patients with adequate organ function sequentially received two cycles of induction chemotherapy (ifosfamide, 1.5 g/m$^2$, d1–3; etoposide, 70 mg/m$^2$, d1–3; and cisplatin, 30 mg/m$^2$, d1–3; repeated every 4 weeks), radiotherapy, and four cycles of consolidation chemotherapy. However, in clinical practice, this might be adjusted according to the patient's organ function and/or the physician's preference. Induction and/or consolidation chemotherapy was omitted in patients with inadequate organ function.

Regarding the radiation volume, either focal radiotherapy (FR) (≥ 54 Gy) or craniospinal irradiation (CSI) (30 Gy) with boost (≥ 24 Gy) was considered for patients with non-germinomatous germ cell tumours (NGGCTs) with nonmetastatic disease until whole-brain radiotherapy (WBRT) (30 Gy) with boost (≥ 24 Gy) became the standard of care at our institution in 2008. Subsequently, CSI plus boost therapy was reserved for patients with metastatic disease. Since 2017, WBRT has been gradually replaced with whole-ventricular irradiation (WVI). The gross target volume (GTV) was defined as the extent of the primary tumour(s) before treatment. The clinical target volume was obtained by adding 1–2 cm to the GTV.

Surgical interventions were primarily reserved for residual disease at the time of response evaluation. However, it would be initially applied if the tumour was resectable and/or there were tumour-related complications.

Routine follow-up assessments were performed every 3–6 months for the first 2 years and every 6–12 months for the next 3 years.

**Statistical analysis**

IBM SPSS Statistics for iOS version 26.0 was used to perform data analyses. The Kaplan–Meier method was used to estimate survival. Disease relapse was defined as an elevation of tumour marker levels in the serum and/or CSF level, appearance of any new lesions on radiographic examinations, or both. An event was defined as disease relapse or death from any cause. Event-free survival (EFS) was calculated from the date of diagnosis to the date of event. OS was determined from the date of diagnosis to the date of death or last follow-up visit. Log-rank tests were used to compare the survival curves. Cox regression analysis was used in the multivariate analysis. All statistical analyses were performed at a significance level of 0.05, and all statistical tests were two-sided.

**Results**

Patient characteristics

A total of 76 patients were eligible for the current study, including 27 with sellar origin, 20 with pineal origin, 18 with basal ganglia origin, and 11 with bifocal origin (Table 1). The median age of the patients
was 12 years (range, 4–26 years). The median serum β-HCG level was 1383.6 IU/L (range, 97.61–31658 IU/L). Thirty-seven patients had elevated serum AFP level at the same time, with median level of 97.1 ng/mL (range, 7.26–2446 ng/mL). CSF was available in 45 patients, with a median β-HCG level of 4606 IU/L (range, 10.24–21454 IU/L). CSF AFP level was elevated in 21 patients, with a median value of 76 ng/mL (range, 7.84–538 ng/mL). Among the 54 patients with available radiological information at our institution at the time of diagnosis, 25 were identified as having intratumoral haemorrhage at diagnosis. Three of the 76 patients developed intratumoral haemorrhage during the clinical course.
Table 1
Patient characteristics:

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N = 76</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>12 years</td>
<td>Range 4–26 years</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>54</td>
<td>71.1</td>
</tr>
<tr>
<td>Female</td>
<td>22</td>
<td>28.9</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sellar</td>
<td>27 (1)*</td>
<td>35.5</td>
</tr>
<tr>
<td>Pineal</td>
<td>20 (1)</td>
<td>26.3</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>18 (1)</td>
<td>23.7</td>
</tr>
<tr>
<td>Bifocal</td>
<td>11</td>
<td>14.5</td>
</tr>
<tr>
<td>Sellar + pineal</td>
<td>10 (5)</td>
<td></td>
</tr>
<tr>
<td>Sellar + basal ganglia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>β-HCG level (IU/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum (n = 76)</td>
<td>1383.6</td>
<td>Range 97.61 to 31658</td>
</tr>
<tr>
<td>CSF (n = 45)</td>
<td>4606</td>
<td>Range 10.24 to 21454</td>
</tr>
<tr>
<td>AFP elevation (ng/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum (n = 37)</td>
<td>97.1</td>
<td>Range 7.26 to 2446</td>
</tr>
<tr>
<td>CSF (n = 21)</td>
<td>76</td>
<td>Range 7.84 to 583</td>
</tr>
<tr>
<td>Radiation field</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FR</td>
<td>1</td>
<td>3.0</td>
</tr>
<tr>
<td>WVI + boost</td>
<td>1</td>
<td>15.9</td>
</tr>
<tr>
<td>WBRT + boost</td>
<td>49</td>
<td>60.5</td>
</tr>
<tr>
<td>CSI + boost</td>
<td>21</td>
<td>20.6</td>
</tr>
<tr>
<td>Median radiation dose</td>
<td>54Gy</td>
<td>Range 30Gy- 60Gy</td>
</tr>
<tr>
<td>Median chemotherapy cycles</td>
<td>5</td>
<td>Range 0–9</td>
</tr>
</tbody>
</table>

Abbreviations: beta-human chorionic gonadotropin, β-HCG; alpha-fetoprotein, AFP; cerebrospinal fluid CSF; focal radiotherapy, FR; whole-ventricular irradiation; whole-brain radiotherapy, WBRT; craniospinal irradiation, CSI

*Number in the blanket represents patients with metastasis at presentation.
In terms of treatment, 11 patients underwent surgery as the initial treatment, followed by chemoradiotherapy. Four patients were treated with initial radiotherapy, whereas 61 patients received initial chemotherapy. Of the 61 patients who received chemotherapy as initial treatment, 12 underwent second-look surgery due to residual disease. By the end of November 2021, 11 patients were lost to follow-up at the last visit. The median follow-up duration for the entire series was 63 months (range, 6–188 months). There were 16 events including 14 relapses and two early deaths (one achieved partial response after two cycles of induction chemotherapy but died before radiotherapy because of emergency tumoral haemorrhage). The other patient underwent second-look surgery due to stable disease after induction chemotherapy but died due to electrolyte imbalance after two additional cycles of consolidation chemotherapy before radiotherapy.) The 5-year EFS and OS rates were 81.5% and 84.1%, respectively (Fig. 1). Moreover, survival differences were comparable between those diagnosed based on histology or β-HCG level elevation (data not shown).

**Surgery**

Surgery was performed in 23 patients. It was initially performed in 11 patients (10 gross total resections, 1 subtotal resection) and applied as a second-look procedure in 12 patients (all gross total resections). To explore the role of surgery, we grouped patients for the survival analysis. Group 1 included patients who underwent surgery as initial treatment (n = 11). Group 2 included patients who achieved complete response (CR) after radiotherapy (n = 4) or induction chemotherapy (n = 35). Group 3 included patients who achieved partial response (PR) after induction chemotherapy and underwent subsequent second-look surgery for residual disease (n = 6). Group 4 included patients with stable disease (SD) or progressive disease (PD) after induction chemotherapy who underwent second-look surgery (n = 6). Group 5 included patients who achieved PR (n = 12) or PD (n = 2) but did not undergo second-look surgery.

The EFS of group 2 was superior to that of group 4 (p = 0.004). Additionally, the significance reached a marginal level between groups 1 and 4 (p = 0.07) and between groups 3 and 4 (p = 0.055). When it comes to the OS, the differences were significant for the above three comparisons. However, the differences between the other groups were not significant in terms of either EFS or OS (Fig. 2).

**Chemotherapy**
In patients who underwent initial surgery (n = 11), four patients did not receive subsequent chemotherapy but received radiotherapy only (Table 2). The other seven patients received chemoradiotherapy. For patients who received radiotherapy as the initial treatment (n = 4), three of four received chemotherapy after completion of radiotherapy. Only one patient did not receive chemotherapy because of inadequate organ function. Overall, 61 patients received chemotherapy as initial treatment. CR was achieved in 35 patients (57.4%), PR in 18 patients (29.5%), SD in two patients (3.3%), and PD in six patients (9.8%), respectively. The total response rate was 86.9%. The median number of chemotherapy cycles was five for the whole series (range, 0–9). Compared with patients who received ≤ 4 cycles of chemotherapy, those who received > 4 cycles showed better survival, in terms of either EFS (p = 0.058) or OS (p = 0.044).

## Table 2
Treatments summary of the whole series

<table>
<thead>
<tr>
<th>Initial treatment</th>
<th>Subsequent treatments</th>
<th>Second-look surgery</th>
<th>Radiotherapy only</th>
<th>Chemotherapy only</th>
<th>Chemotherapy + radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery (n = 11)</td>
<td></td>
<td>-</td>
<td>4</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>Radiotherapy (n = 4)</td>
<td></td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Chemotherapy (n = 61)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR (n = 35)</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>35</td>
</tr>
<tr>
<td>PR (n = 18)</td>
<td></td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>SD (n = 2)</td>
<td></td>
<td>2</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PD (n = 6)</td>
<td></td>
<td>4</td>
<td>3</td>
<td>-</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: complete response CR; partial response PR; stable disease SD; progressed disease PD

### Radiotherapy

Except for two early deaths, all patients received radiotherapy, including one FR, one WVI, 49 WBRT, and 23 CSI. In patients without metastasis at presentation (n = 66), the efficacy was comparable between CSI and non-CSI, in terms of either EFS (p = 0.50) or OS (p = 0.66). The median radiation dose was 54 Gy (range, 30–60 Gy) for the entire series. Except for those who received radiotherapy as salvage therapy (PD after initial chemotherapy), the prescription doses were ≥ 54 Gy in 43 patients and < 54 Gy in 25 patients. Survival analyses did not reveal any differences in EFS (p = 0.87) or OS (p = 0.98).

### Multivariate analysis

To further explore the impact of clinical factors on survival, we performed multivariate analysis. Patients who had early death or PD after induction chemotherapy were excluded from the study. Clinical factors
included sex (male vs. female), age, metastasis (yes vs. no), surgery (yes vs. no), radiation volume (CSI vs. non-CSI), radiation dose (≥ 54 Gy vs. <54 Gy), number of chemotherapy cycles (> 4 vs. ≤4), β-HCG level (> 3000 IU/L vs. ≤3000 IU/L), AFP level (elevated vs. normal), and intratumoral haemorrhage during the disease course (yes vs. no). In patients with available tumour markers in both the serum and CSF levels, a higher value was recruited for the analysis. Chemotherapy cycles, β-HCG levels, and intratumoral haemorrhage during the disease course were identified as independent factors for survival. Additional chemotherapy cycles significantly reduced the risk of either disease relapse (hazard ratio [HR] 0.144, p = 0.020) or disease-related death (HR 0.111, p = 0.028). Higher β-HCG levels and intratumoral haemorrhage during the disease course were adverse prognostic factors (Table 3).

Table 3
Multivariate analyses

<table>
<thead>
<tr>
<th>Parameters</th>
<th>EFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age (con.)</td>
<td>0.982</td>
<td>0.845–1.142</td>
</tr>
<tr>
<td>Gender (Female vs. Male)</td>
<td>1.853</td>
<td>0.338–10.172</td>
</tr>
<tr>
<td>Metastasis (Yes vs. No)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Surgery (Yes vs. No)</td>
<td>0.256</td>
<td>0.028–2.338</td>
</tr>
<tr>
<td>Radiotherapy volume (CSI vs. non-CSI)</td>
<td>1.902</td>
<td>0.177–20.442</td>
</tr>
<tr>
<td>Radiation dose (≥ 54Gy vs. &lt;54Gy)</td>
<td>2.719</td>
<td>0.389–19.012</td>
</tr>
<tr>
<td>Cycles of chemotherapy (&gt; 4 vs. ≤4)</td>
<td>0.144</td>
<td>0.028–0.740</td>
</tr>
<tr>
<td>β-HCG level (&gt; 3000 vs. ≤3000)</td>
<td>4.342</td>
<td>0.948–19.890</td>
</tr>
<tr>
<td>AFP level (Elevated vs. Normal)</td>
<td>0.762</td>
<td>0.171–3.389</td>
</tr>
<tr>
<td>Hemorrhage during course (Yes vs. No)</td>
<td>35.887</td>
<td>2.844–452.871</td>
</tr>
</tbody>
</table>

Abbreviations: beta-human chorionic gonadotropin, β-HCG; alpha-fetoprotein, AFP; event-free survival EFS; overall survival OS; craniospinal irradiation CSI; hazard ratio HR; confidence interval CI

Discussion
In the current retrospective study, we explored the treatment outcomes in patients with iGCTs with choriocarcinoma element or higher β-HCG level treated with a radiotherapy-based regimen. As indicated, the 5-year EFS and OS rates were > 80%. Furthermore, we identified chemotherapy cycles, β-HCG level, and intratumoral haemorrhage during the clinical course as independent risk factors for survival.

Choriocarcinoma is a rare subtype of NGGCTs. Based on our data, those with choriocarcinoma element or higher β-HCG levels accounted for 5.2% of patients with iGCTs diagnosed during the same period. Many studies have shown that radiotherapy is indispensable for the treatment of iGCTs, for either germinomas or NGGCTs [5–8]. In our cohort, only two patients did not receive radiotherapy due to severe complications. As a result, the 5-year survival rate for the entire series reached 80%, which is superior to that in historical reports. Although irradiation-based regimens have improved patients’ prognosis, the optimal radiation volume remains undetermined. In a study conducted by the International Society of Pediatric Oncology, patients with localised NGGCTs had a 5-year OS of 82% after FR [9]. Based on ACNS 0112 data, the 5-year OS was 93% after CSI [10]. In the ACNS 1123 study, patients who received WVI had a 3-year OS of 92% [11]. It seems that the efficacy is superior in the COG reports in which CSI or WVI was applied. However, the differences were comparable among different volumes for patients with NGGCTs with localised disease in the same cohort [11, 12]. Data from our series also showed that disease control and survival rates were similar between patients treated with CSI or non-CSI. Considering the potential side effects of extended-field irradiation, it is optional to choose non-CSI in this setting if there is no evidence of metastasis.

In terms of radiation dose, most patients in our series received a dose ≥ 54 Gy, as adopted by most groups for patients with NGGCTs. Simultaneously, there were a number of patients whose prescription dose was < 54 Gy. Survival was comparable between the two radiation dose groups, in either the single variate analysis or multivariate analysis. This may be attributed to the small sample size of this study. Interestingly, we also identified two patients who received 40 Gy and five cycles of chemotherapy. One patient underwent initial surgery, and the histology revealed germinoma with sporadic syncytiotrophoblastic element infiltration. The serum β-HCG level was 1032 IU/L. The other patient was diagnosed based on tumour marker level elevation, with a CSF β-HCG level of 997 IU/L. They remained disease-free at the last visit for 105 and 94 months, respectively (Fig. 3). The less aggressive treatment strategy may be decided based on the germinoma histology, homogeneous enhancement of the tumour on radiographic images, and satisfactory response after induction chemotherapy.

Generally, β-HCG is an important marker, with a remarkable elevation indicating the presence of choriocarcinoma element. However, a widely accepted cut-off value has not yet been established. It appears that it is more reliable when it is ≥ 10,000. Conversely, hundreds or even lower could occur, probably caused by the quantity of choriocarcinoma elements [13, 14]. Therefore, it is challenging to determine the presence of choriocarcinoma element based solely on β-HCG level elevation, especially when the elevation is mild to moderate. Otherwise, the individualised treatment strategy, which was determined by malignant elements, is far from established in patients with NGGCTs, even in those with homogeneous element. Thus, a dose of ≥ 54 Gy was unanimously recommended in all patients with
NGGCTs. However, in combination with our data, some issues might be raised: Is there a possibility that
the radiation dose could be reduced in patients with choriocarcinoma or in certain subgroups of patients,
especially those with mild-to-moderate β-HCG level elevation and achieving CR after induction
chemotherapy? Alternatively, in patients with germinoma with full histology evaluation, would it be
necessary to be treated as NGGCTs even if β-HCG level is moderately elevated? Given that β-HCG > 3000
IU/L was identified as an adverse prognostic factor in our series, an aggressive treatment strategy,
including a higher radiation dose, seems more justified in these patients. For those with β-HCG level <
3000 IU/L, more studies are needed to clarify these issues.

Intratumoral haemorrhage is a common complication in patients with choriocarcinoma, which could
occur at any time during the clinical course. Some may occur spontaneously, and some may be
intervention-related, such as haemorrhage after biopsy or radiotherapy [15–21]. Hence, as a major cause
of early death, it is a major concern for clinicians that has a significant influence on decision-making
regarding treatment modality arrangement. However, haemorrhage was not proven to be an independent
factor for survival by far [1, 2]. In our study, patients with or without intratumoral haemorrhage at
diagnosis showed a similar prognosis (data not shown). Although haemorrhage during the course was
identified as an adverse factor in our series, only two patients were included in the model (patients with
early death were excluded from the multivariate analysis), making the conclusion weak. Therefore, for the
entire series, fatal haemorrhage events were not as common as those in the published reports. The
possible reasons may lie in our careful surgical candidate selection and induction chemotherapy
application.

Generally, choriocarcinoma elements are sensitive to antitumor therapy. As indicated in our series, 57.4%
of patients achieved CR after induction chemotherapy. They showed similar survival rates as those
receiving initial surgery. Even in patients with PR after induction chemotherapy, those undergoing second-
look surgery had a good prognosis. Therefore, in patients with choriocarcinoma element, induction
chemotherapy could be considered initially, which may provide some patients with the opportunity to
avoid radical resection. After all, it is always challenging for surgeons to deal with this type of tumour, as
it is characterised by spontaneous haemorrhage. Additionally, gross total resection may be easier to
achieve during second-look surgery because of decreased tumour volume and/or blood supply and
because the extent of resection is an independent factor for survival in patients with choriocarcinoma
element [1, 2]. Probably because of the small sample size, the removal of residual disease was not found
to be correlated with survival in our series.

In the multivariate analysis, we found that chemotherapy cycles were an independent prognostic factor.
Both disease control and survival can be improved by additional cycles of chemotherapy. Given that
choriocarcinoma is characterised by distant metastasis, even beyond the CNS, adequate chemotherapy
may bring survival benefits by eliminating potential micrometastasis, especially in responders [2, 22, 23].
Thus, although the optimal number of chemotherapy cycles is still unknown in this setting, more than
four cycles are warranted in patients with choriocarcinoma element or with higher β-HCG level. However, a
small number of patients do not respond well to ICE-based regimens. Some authors have introduced
high-dose chemotherapy with stem cell support in these patients and reported satisfactory results [22, 24]. Therefore, more aggressive regimens may be recommended, especially in patients with poorer prognosis, as indicated by our study.

Generally, in the current study, we reported better outcomes in patients with choriocarcinoma element or higher β-HCG levels treated with a radiotherapy-based regimen. However, the conclusions may be limited by the retrospective study design and number of cases included. To recruit a large number of cases for the study, β-HCG level > 500 IU/L was set as an inclusion criterion for our study. However, it is still difficult to establish a definite correlation between high β-HCG levels and presence of choriocarcinoma element. Even in those with choriocarcinoma element confirmed by histology, whether it occupied major or minor components was not further analysed. Moreover, the treatments were not consistent for the entire series, such as indications for surgical intervention, radiation dose, and chemotherapy cycles; this resultant bias could not be avoided. Therefore, multicentre collaboration is needed to initiate prospective studies, which is the best way to investigate this rare malignancy.

Declarations

Conflict of Interest: None.

Funding Statement: This work was supported by Beijing Municipal Bureau of Health. (Grant number: PXM2019)

Data Availability Statement for this Work: All data generated and analyzed during this study are included in this published article (and its supplementary information files).

References


Figures
Figure 1

Event-free survival (EFS) and overall survival (OS) for the whole series
Figure 2

Comparison of survival among patients grouped by surgery status. Group 1 included patients who underwent surgery as initial treatment (n=11). Group 2 included patients who achieved complete response (CR) after radiotherapy or induction chemotherapy (n=39). Group 3 included patients who achieved partial response (PR) after induction chemotherapy and underwent subsequent second-look surgery for residual disease (n=6). Group 4 included patients who had stable disease (SD)/progressive
disease (PD) after induction chemotherapy and underwent second-look surgery (n=6). Moreover, group 5 included patients who achieved PR (n=12) or PD (n=2) but did not underwent second-look surgery. (A) EFS comparison. (B) OS comparison.

Figure 3

Representative cases. A/B were images of a 21-year old man who was diagnosed with pineal intracranial germ cell tumour based on beta human chorionic gonadotropin (β-HCG) level elevation in both the serum (185 IU/L) and cerebral spinal fluid (997 IU/L) in December 2013. Figure A shows primary pineal lesion and metastasis at the dorsal medulla oblongata (white arrows). Figure B shows CT image that reveals dissemination around the frontal horns of the lateral ventricle (white arrows). He achieved complete response after two cycles of chemotherapy. Then, subsequent CSI with prescription dose of 40 Gy and three cycles of consolidation chemotherapy was applied. Figure C shows CT image of a 15-year-old boy, revealing left basal ganglia lesion at diagnosis (white arrow) with serum β-HCG level of 1032 IU/L in February 2013. He underwent surgery initially, and the histology was germinoma with sporadic syncytiotrophoblastic element infiltration. Figure D shows post-surgery image (white arrow, surgery cavity). Figure E was the representative image of H&E staining (black arrows, syncytiotrophoblastic cells). AFP and CD30 were absent in this tumour (F-G). The syncytiotrophoblastic component expressed β-HCG
(H), while primordial tumour cells were immunopositive for OCT4 and PLAP (I-J). After two cycles of chemotherapy, he received whole-brain radiotherapy with prescription dose of 40 Gy and subsequent three cycles of chemotherapy. Both patients were disease-free in November 2021.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementarytable.xlsx](#)