The Analysis of Outcomes of Intracranial Germ Cell Tumors: A Single-institute Study

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Abstract

**Purpose:** For analyzing the epidemiology and treatment according to the KSPNO protocol results of germ cell tumor patients at our institution.

**Methods:** From 2004 to 2019, of 6494 patients with intracranial neoplasms, 61 (0.9%) patients with iGCTs were enrolled. Pediatric patients underwent chemotherapy and radiotherapy according to the Korean Society for Pediatric Neuro-Oncology (KSPNO) protocol, and adult patients were treated with bleomycin, etoposide, and cisplatin (BEP) regimens. Survival rates, recurrence rates, and posttreatment morbidity were analyzed to identify risk factors.

**Results:** The median age was 20.0 years (range: 1-42), and the follow-up duration was 77.7 months (range: 10.0-203.4 months). The tumors developed most frequently in the pineal gland (49.2%). There were no significant differences in outcomes between protocols, but the KSPNO protocol group had lower tumor recurrence (14.8% vs. 17.6%, p=0.524) and mortality rates (0% vs. 5.9%, p=0.307) than the other groups. According to the pathological subtype, the outcomes were significantly different between the germinoma and nongerminomatous germ cell tumor (NGGCT) groups. The 10-year progression-free survival rates were 93.2% and 67.1% in the germinoma and NGGCT groups, respectively (p = 0.009). The NGGCT pathological type (p=0.021) was a significant recurrence-associated factor in the multivariate analysis. Significant adverse occurred in 14 patients (7 patients in each group).

**Conclusions:** Pure germinomas have a higher survival and lower recurrence rate than NGGCTs. A multidisciplinary approach is needed to select appropriate iGCT treatments, and reducing the radiation dose could minimize posttreatment morbidity.

**Clinical trial registration**

Not applicable

**Introduction**

Intracranial germ cell tumors (iGCTs) are sensitive to chemotherapy and radiation therapy (RT). For germinomas and central nervous system (CNS) germinomas, the 10-year overall survival (OS) is reported to be approximately 90% [1]. Prior to the era of chemotherapy and radiation combination therapy, treatment at the primary site alone was a common practice, and the applied radiation dose frequently exceeded 50 Gy. [2,3]. However, following long-term follow-up, radiotherapy-induced secondary brain tumors and malignancies were reported, although rarely [4-7].

Radiation-induced complications after treatment may be inevitable, but many investigators have attempted to reduce the radiation dose and increase the role of chemotherapy to minimize these complications [1,8-11]. Since the Korean Society for Pediatric Neuro-Oncology (KSPNO) G-081/G-082 clinical trial was introduced in 2009, our institute has applied this protocol to patients with iGCT. The aim
of the KSPNO is to reduce the radiation dose while maximizing the cure rate to improve the quality of life of survivors.

This study aims to analyze the epidemiology of iGCTs, including OS, and progression-free survival (PFS), based on the experiences of our institution and to analyze the factors affecting them. Therefore, we discuss the effectiveness and safety of the new protocol.

**Materials And Methods**

We retrospectively reviewed the electronic medical records (EMRs) of consecutively enrolled patients with histologically and clinically diagnosed germ cell tumors from 2004 to 2019 in our institute. Patients who were diagnosed with and treated for iGCTs for more than six months were included. Of the 65 patients diagnosed with iGCTs in our institution, two patients had insufficient medical records and two patients had incomplete or were lost to follow-up; Finally, 61 patients were included in the study. The primary outcome was OS, defined as the period from the date of surgery or tissue biopsy to the time of death or the last follow-up of the patient. The secondary outcome, PFS, was defined as the period from the date of surgery or biopsy to the date of disease progression confirmed by a follow-up magnetic resonance imaging (MRI) scan. In the absence of evidence of progression, the OS and intervals were considered equal. Significant adverse events occurring during chemotherapy were defined as grade 3 or higher based on the common terminology criteria for adverse events (CTCAE) version 5.0. Statistical analyses were performed using logistic regression and Kaplan-Meier survival analysis. Additionally, these analyses were conducted using SPSS version 21 (IBM Corp., Armonk, NY, USA).

Pure germinoma diagnosed since 2009 was treated with the KSPNO G-081 protocol, and NGGCT was treated with the KSPNO G-082 protocol. Treatment response was evaluated at 3-4 weeks after the last cycle of chemotherapy and three months after completion of radiation therapy with MRI. 1) Complete remission: All lesions are not visible on MRI and positive cytology becomes negative (β-HCG (if > 10) declines to <2 μU/ml). 2) Partial response (PR): Tumor volume decrease ≥ 50 % of pretreatment volume. 3) Stable disease (SD): Neither sufficient decrease in tumor volume for PR, nor sufficient increase in tumor volume for PD. 4) Progressive disease (PD): Tumor volume increase ≥ 25 % of pretreatment volume.

Solitary germinomas were treated with chemotherapy and radiation, and local RT was performed without craniospinal irradiation (CSI) if there was a CR. For multiple or disseminated germinomas, CSI was applied in all cases, and the lowest dose was applied until CR. In the NGGCT group, chemotherapy and radiotherapy were applied for both localized and disseminated tumors; radiotherapy was applied at 36 Gy for localized lesions and 39 Gy for disseminated lesions according to the KSPNO-G082 protocol. Bleomycin, etoposide, and cisplatin (BEP) regimens were administered to middle-aged adults or pediatric patients before the KSPNO protocol. This study protocol was approved by the institutional review of the board (IRB No. 2021-01-016), and the need for informed consent was waived.
Results

Between 2004 and 2019, 65 (1.05%) of the 6394 patients diagnosed and treated with intracranial tumors in SNUBH were diagnosed with iGCTs. Four patients with insufficient EMRs or less than six months of follow-up were excluded. The general characteristics of the patients are summarized in Table 1. Finally, 61 patients were enrolled. The median follow-up period was 77.7 months (range, 10-203.4 months). Males were dominant (M:F = 4.08:1), and the mean age was 20 years (range: 1-42 years). The tumor developed most frequently in the pineal area (n = 30, 49.2%). Pathologically, 39 (63.9%) patients were diagnosed with germinoma, and 22 (36.1%) patients were diagnosed with NGGCT. Fifty-three of the 61 patients (86.9%) received adjuvant radiation treatment. The median CSI dose was 29.4 Gy (range: 13-39), and the local boost dose was 19.8 Gy (range: 10.8-54 Gy). The median dose of whole-brain or ventricle radiation was 30.0 Gy (range: 5.4-50.4 Gy) and that of in the KSPNO group were 23.4 Gy which was lower dose than those in the other protocol groups (median: 30.4 Gy) (p = 0.016).

Twenty-seven out of 61 (44.3%) patients were treated according to the KSPNO protocol. Two patients discontinued treatment; one was achieved with 1A and 1B cycles and dropped, and the other was identified as having progressive disease during the 1A cycle, so chemotherapy was discontinued. Twenty-three adults (germinoma = 15, NGGCT = 8) and 12 children (germinoma = 6, NGGCT = 6) were diagnosed before the KSPNO protocol.

The Kaplan-Meier survival curves of PFS and OS are illustrated in Figs. 1 and 2. The mean PFS was 169.7 months (range: 1.2-203.4 months), and the mean OS was 196.6 months (range: 10-203.4 months). Ten patients (16.4%) relapsed after treatment. According to the treatment protocol, the KSPNO protocol group showed a lower recurrence rate than the other groups, but this difference was not statistically significant (11.5% vs. 20.0%, p = 0.494). According to the pathological type, the germinoma group showed better PFS than the NGGCT group, and this difference was statistically significant (10-year PFS, 93.2% vs. 67.8%, p = 0.011). The total number of survivors was 59 (96.7%) during the follow-up period.

There were no significant differences in OS between treatment protocols (p = 0.257); however, according to pathological type, there was a marginal difference (10-year OS of germinoma vs. NGGCT: 100% vs. 90%, p = 0.056). Two patients in the NGGCT group were diagnosed with mature teratoma and choriocarcinoma (Table 2). Mature teratoma patients died of cholecystitis and septic shock after cholecystectomy, and choriocarcinoma patients died of complications associated with disease progression. The morbidity persisted after treatment in 35 (57.4%) patients. The most common symptoms in patients were hormonal disturbances (n = 16, 26.2%) requiring hormonal replacement, visual disturbance (n = 10, 16.4%), cognitive dysfunction (n = 7, 11.5%), and hydrocephalus (n = 6, 9.8%). Of the 54 patients treated with chemotherapy, 14 patients (25.9%) had CTCAE grade 3 or higher (Table 3). The most common adverse events, related to the blood and lymphatic systems, occurred in 13 patients, most of whom had neutropenic fever. There was no difference in toxicity between the two groups according to the treatment protocol (p = 0.528). The only significant factor in the univariate (p = 0.032)
and multivariate (p = 0.027) analyses was pathological type. The odds ratio of the NGGCT group was 5.82 (95% CI, 1.221-25.512), indicating this factor was related to relapse.

**Discussion**

CNS GCTs are prevalent in children and adolescents in eastern Asia but are generally rare tumors that account for 2-3% of all primary intracranial tumors [12-16]. These tumors are radiosensitive and curable with radiotherapy alone, with a cure rate of 72-100% [17-22]. These tumors may require neurosurgical interventions, such as debulking or pathological confirmation, and cause tumor-related hydrocephalus. These treatment options offer a multidisciplinary approach to CNS GCT treatment. However, for this reason, patients admitted to institutions that do not practice an active multidisciplinary approach may be treated with different treatment protocols depending on the department they are admitted to.

The KSPNO released the KSPNO-G081/G082 protocols in 2009. Since then, the authors have applied this protocol to patients at the SNUBH. The results of a relatively homogenous group of patients who underwent the KSPNO protocol was used to diagnose a consecutive patient, and the patient’s multidisciplinary treatment process was shared among departments through outpatient clinics and institutional conferences. In this study, the authors compared and analyzed the KSPNO protocol group and other protocol groups. All of the patients’ clinical information was shared among departments through outpatient clinics and institutional conferences, with a multidisciplinary approach. This study is meaningful for verifying the effectiveness and safety of the KSPNO protocol.

In recent decades, radiation doses applied to primary sites exceeded 50 Gy [2,3]. However, the histological identity between CNS germinoma, seminoma of the testis, and dysgerminoma of the ovary suggest the possibility of application at a dose of 25-30 Gy, the therapeutic dose used in these tumors, for CNS germinoma [20]. In addition, Aydin et al. reported CR at autopsy after treatment of CNS pure germinoma with only 16 Gy of radiation[23]. Some studies have suggested that doses can be reduced to less than 36 Gy in whole-ventricular irradiation without preirradiation chemotherapy [24,25].

There was a report that radiotherapy alone was associated with the risk of new CNS germinoma relapse [26]. In addition, CNS germinoma is reported to have a 10-year OS rate of 90% [1]. Radiation-induced secondary brain tumors and subsequent malignant neoplasms caused by RT are rare, but there are some reported cases [4-7]. In addition, the cumulative risk of brain tumors obtained after 15 years of cranial irradiation has been reported to be 2.7% [5].

CNS germinoma is known to be susceptible to radiation as well as chemotherapy, and platinum-based chemotherapy reduces late complications associated with RT, and allows a reduction in therapeutic radiation doses to 24-30 Gy without reducing the therapeutic effect [1,8-11]. However, some studies have reported treatment failure due to limited irradiation fields for localized germinoma compared to those for the whole ventricle [27-29].
The KSPNO protocol uses neoadjuvant chemotherapy to maintain a curative effect while applying a reduced radiation dose. Recent consensus suggests that at least the whole ventricle should be treated and irradiated to reduce the risk of local relapse of germinoma [1]. As described above, there have been reports on applying chemotherapy and combination therapy to determine whether CSI is necessary according to the treatment response, reduce the final radiation dose and reduce complications related to radiation in the long term [30-34].

Adverse events in the KSPNO protocol group were not significantly different from those in the other protocol groups. In addition, mortality was 0% in the KSPNO protocol group and 5.7% in the remaining subgroups (p = 0.503). These results show that the KSPNO protocol is acceptable in comparison with conventional treatment.

A significant number of germinomas occur in the pineal, sellar, and suprasellar areas. Therefore, it is crucial to reduce nephrotoxicity because patients often experience diabetes insipidus (DI) before treatment. Cisplatin, which was used in the traditional regimen, was replaced with carboplatin in the KSPNO protocol, which may reduce urotoxicity compared to traditional therapy. However, cyclophosphamide also has urotoxic properties, so mesna (sodium 2-mercaptoethanol sulfonate) should be added [31,35]. The results of the current study revealed that this goal was achieved. The adverse events that occurred in the patients in the KSPNO protocol group were mostly blood and lymphatic system problems, and there were no patients with signs and symptoms of urotoxicity. Moreover, there was one patient in a different protocol group with CTCAE grade 3 urotoxicity. A similar result to that in the current study was reported in another study using the KSPNO protocol [31].

Single chemotherapy regimens for NGGCTs, such as radiotherapy alone, show modest or even inferior effectiveness [36,37]. However, combined chemotherapy and RT may provide comparable germinoma control at lower radiation doses and field volumes than those applied in RT alone [38-42]. In addition, one of the critical benefits of chemotherapy for NGGCTs is that it reduces tumor size and vascularity before surgery [1].

The therapeutic effect of CSI is controversial. The benefit of CSI in patients diagnosed with germinoma is reported to be approximately 15% [43]. Relapses along the neuraxis outside the radiation field are rare, and the improvement in the outcomes with CSI was not significantly different [44]. In our study, the mean PFS was longer in the germinoma group (169.68 months) than in the other group (188.54 months) (p = 0.215). In NGGCT, however, the opposite trend (149.0 vs. 107.8 months, p = 0.831) showed that there was no significant difference according to whether CSI was applied.

Our study has some limitations, and this requires cautious interpretation of the results. Since the introduction of the KSPNO-G081/G082 protocols in 2009, 26 pediatric patients have undergone the KSPNO protocol and were included in our study. The KSPNO protocol group (23.4 Gy; range, 5.4-30.6 Gy) was treated with lower doses of whole-ventricle irradiation than the other treatment protocol groups (33.3 Gy; range, 19.8-50.4 Gy), but there were no significant differences in outcomes such as OS and PFS. However, the patients in the KSPNO protocol group were significantly younger than those in the other
protocol groups. Moreover, because of the rarity of the disease, the group size may not be enough to elucidate statistical significance. These limitations should be complemented by long-term follow-up studies with larger sample sizes.

**Conclusions**

Pathologic type is a significant prognostic factor of outcomes in CNS germ cell tumor patients. For these tumors, surgical removal is considered to be practical and meaningful for histological diagnosis, and the KSPNO protocol with prophylactic neoadjuvant chemotherapy and a reduced radiation dose seems to be a viable treatment option. For appropriate treatment of iGCTs, a multidisciplinary approach may be needed.

**Declarations**

**Acknowledgments**

Not applicable

**Declarations**

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**Conflicts of interest**

The authors declare that they have no conflict of interest

**Consent to participate**

The authors have read and approved the manuscript.

**Consent to publish**

Authors agreed to be published in this manuscript.

**Availability of data and material**

**Code availability**

Not applicable

**Authors' contributions**
CYK designed the study; KOG, KH, JHH, and CYK created the data; CYK, KH, and KOG analyzed the data and wrote the draft; HSC, YJK, BSC, IAK, GC, BKC, CYK reviewed the manuscript and edited; KOG administrated the project.

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Tables

Table 1. Summary of the general characteristics of the subjects according to the treatment protocols.
| Protocol                        | Total (n=61) | KSPNO (n=26) | Others (n=35) | p-value |
|--------------------------------|--------------|--------------|--------------|---------|
| Sex, M:F                       | 49:12        | 22:4         | 27:8         | 0.302   |
| Median age, month (range)      | 20 (1-42)    | 15 (6-24)    | 21 (1-42)    | <0.001* |
| Tumor location (n, %)          |              |              |              | 0.416   |
| Pineal gland                   | 30 (49.2)    | 15 (57.7)    | 15 (42.9)    |         |
| Sellar and suprasellar         | 12 (19.7)    | 5 (19.2)     | 7 (20.0)     |         |
| Cerebrum                       | 4 (6.6)      | 1 (3.8)      | 3 (8.6)      |         |
| Intraventricular               | 2 (3.3)      | 0            | 2 (5.7)      |         |
| Thalamostriate                 | 2 (3.3)      | 2 (7.7)      | 0            |         |
| Disseminate                    | 2 (3.3)      | 1 (3.8)      | 1 (2.9)      |         |
| Multifocal                     | 7 (11.5)     | 2 (7.7)      | 5 (14.3)     |         |
| Others                         | 2 (3.3)      | 0            | 2 (5.7)      |         |
| Pathological type (n, %)       |              |              |              | 0.450   |
| Germinomatous                  | 39 (63.9)    | 17 (65.4)    | 21 (61.8)    |         |
| NGGCT                          | 22 (36.1)    | 9 (34.6)     | 13 (38.2)    |         |
| Chemotherapy, n (%)            | 56 (91.8)    | 26 (100)     | 30 (85.7)    |         |
| RT, n (%)                      | 53 (86.9)    | 25 (96.2)    | 28 (80.0)    |         |
| aCSI                           | 29.4 (13-39) | 25.2 (13-39) | 30.3 (19-36) | 0.347   |
| aWB or WV                      | 30.0 (5.4-50.4) | 23.4 (5.4-30.6) | 33.3 (19.8-50.4) | 0.006* |
| aLocal                         | 19.8 (10.8-54) | 18.9 (10.8-54) | 19.8 (12.6-40) | 0.608   |
| Median follow-up duration (range, months) | 77.7 (10.0-203.4) | 68.9 (10.0-182.1) | 92.0 (12.1-203.4) | 0.109   |
| Mean PFS                       | 169.7        | 156.8        | 164.0        | 0.495   |
| Mean OS                        | 196.6        | b_           | 192.3        | 0.257   |
| Recurrence                     | 10 (16.4%)   | 3 (11.5%)    | 7 (20.0%)    | 0.494   |
| Mortality                      | 2 (3.3%)     | 0            | 2 (5.7%)     | 0.503   |
| Comorbidity                    | 35 (57.4%)   | 14 (53.8%)   | 21 (60.0%)   | 0.413   |
| Hormonal disturbance           | 16           | 6            | 10           |         |
| Visual disturbance             | 10           | 4            | 6            |         |
Cognitive dysfunction 7 3 4
Hydrocephalus 6 2 4
Others 6 3 3

KSPNO The Korean Society for Pediatric Neuro-Oncology, NGGCT nongerminomatous germ cell tumor, CSI craniospinal irradiation, WB whole-brain radiotherapy, WV whole-ventricle radiotherapy

a Values as a radiotherapy dose in Gy, (range)

b All the patients in the KSPNO protocol group were alive at the last follow-up, so no statistics were calculated.

*p<0.05

Table 2. Tumor distributions according to pathological type.

|                | Total (%) | KSPNO     | Others    |
|----------------|-----------|-----------|-----------|
| Germinoma      | 39 (63.9%)| 17 (65.4%)| 22 (62.9%)|
| NGGCT          | 22 (36.1%)| 9 (34.6%) | 13 (37.1%)|
| Mature teratoma| 7 (11.5%) | 1 (3.8%)  | 6 (17.1%) |
| Mixed GCT      | 7 (11.5%) | 4 (15.4%) | 3 (8.6%)  |
| Choriocarcinoma| 3 (4.9%)  | 1 (3.8%)  | 2 (5.7%)  |
| Immature teratoma| 1 (1.6%) | 1 (3.8%)  | 0         |
| NOS            | 4 (6.6%)  | 2 (7.7%)  | 2 (5.7%)  |

KSPNO The Korean Society for Pediatric Neuro-Oncology, NGGCT nongerminomatous germ cell tumor, GCT germ cell tumor, NOS not otherwise specified

Table 3. Adverse events during treatment.
| CTCAE (v5.0) grade ≥ 3 | p-value |
|------------------------|---------|
|                        | KSPNO (n=26) | Others (n=29) | Total |
| Blood and lymphatic system | 6 4 13 |            |
| Musculocutaneous | a1 0 1 |            |
| Respiratory | 1 0 1 |            |
| Renal and Urinary | 0 1 b1 |            |
| Nervous system | 0 2 2 |            |
| Total | 7 (26.9%) 7 (24.1%) 14 (25.9%) | 0.528 |

CTCAE Common Terminology Criteria for Adverse Events, KSPNO The Korean Society for Pediatric Neuro-Oncology

a Overlap with blood and lymphatic system

b Overlap with nervous system