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Original Article

The clinical characteristics and treatment outcome of 57 children and adolescents with primary central nervous system germ cell tumors

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Abstract

Primary central nervous system germ cell tumors (CNS-GCTs) in children and adolescents have unique clinical features and methods of treatment compared with those in adults. There is little information about Chinese children and adolescents with CNS-GCTs. Therefore, in this study we retrospectively analyzed the clinical features and treatment outcome of Chinese children and adolescents with primary CNS-GCTs. Between January 2002 and December 2012, 57 untreated patients from a single institution were enrolled. They were diagnosed with CNS-GCTs after pathologic or clinical assessment. Of the 57 patients, 41 were males and 16 were females, with a median age of 12.8 years (range, 2.7 to 18.0 years) at diagnosis; 43 (75.4%) had non-germinomatous germ cell tumors (NGGCTs) and 14 (24.6%) had germinomas; 44 (77.2%) had localized disease and 13 (22.8%) had extensive lesions. Fifty-three patients completed the prescribed treatment, of which 18 underwent monotherapy of surgery, radiotherapy, or chemotherapy, and 35 underwent multimodality therapies that included radiotherapy combined with chemotherapy or surgery combined with chemotherapy and/or radiotherapy. PEB (cisplatin, etoposide, and bleomycin) protocol was the major chemotherapy regimen. The median follow-up time was 32.3 months (range, 1.2 to 139 months). Fourteen patients died of relapse or disease progression. The 3-year event-free survival (EFS) and overall survival rates for all patients were 72.2% and 73.8%, respectively. The 3-year EFS was 92.9% for germinomas and 64.8% for NGGCTs ($P = 0.064$). The 3-year EFS rates for patients with NGGCTs who underwent monotherapy and multimodality therapies were 50.6% and 73.5%, respectively ($P = 0.042$). Our results indicate that multimodality therapies including chemotherapy plus radiotherapy were better treatment option for children and adolescents with CNS-GCTs.

Key words Primary central nervous system germ cell tumors, chemotherapy, radiotherapy, survival rate, children

Primary central nervous system germ cell tumors (CNS-GCTs) are rare, constituting 3%–14% of all brain tumors in children and adolescents. They are most common in the second decade of life and have a male predominance, with a reported male-to-female ratio of 3–4 to 1[1-3]. In contrast to western counties, CNS-GCTs are frequent in East Asia; the incidence is 14% in Taiwan, 11.2% in Korea, 3.3% in Canada, 3.5% in France, and 4.1% in America, indicating that both genetic and environmental factors play vital roles in the development of these tumors[2-6]. The World Health Organization has classified CNS-GCTs into germinomas and non-germinomatous germ cell tumors (NGGCTs), and NGGCTs are subdivided into teratoma (mature and immature), embryonal carcinoma, choriocarcinoma, yolk-sac tumor (endodermal sinus tumor), and mixed tumors[4-6]. Treatment outcome of CNS-GCTs has been improved by using multimodality therapies including chemotherapy plus radiotherapy. The 5-year

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overall survival (OS) rate is more than 90% for germinomas and 70% for NGGCTs[7-9].

CNS-GCTs usually originate from the pineal and suprasellar regions of the brain, which makes excision or biopsy difficult and highly risky, leaving many patients without a pathologic diagnosis. Nevertheless, NGGCTs, with the exception of mature teratoma, could secrete alpha fetoprotein (AFP) and/or human chorionic gonadotropin (HCG), and these tumor markers can be detected in the serum and/or cerebrospinal fluid (CSF) of patients with CNS-GCTs. In western countries, elevated tumor markers contribute to the diagnosis of secreting CNS-GCTs. A secreting CNS-GCT was defined as AFP levels greater than 25 ng/mL or β-HCG levels greater than 50 IU/L in blood and/or CSF, which act as markers for diagnosis and monitoring disease response. Moreover, secreting CNS-GCTs do not need biopsy[10], but for germinomas and mature teratoma with normal tumor markers, pathologic diagnosis is very important.

In China, the diagnosis and treatment methods of CNS-GCTs vary greatly in different hospitals. There is little information about clinical characteristics and treatment outcome of Chinese children and adolescents with CNS-GCTs. In this study, we retrospectively analyzed the clinical features and treatment outcome, and compared the results of monotherapy with multimodality therapies in Chinese children and adolescents with CNS-GCTs.

Patients and Methods

Patients

All patients with untreated primary CNS-GCTs who were first presented to and received treatment at the Sun Yat-sen University Cancer Center between January 2002 and December 2012 were included in this study.

Diagnostic criteria

Diagnosis was determined according to the histopathology and/or clinical manifestations, combined with imaging findings and the levels of tumor markers[7-9]. For both germinomas and NGGCTs, pathologic diagnosis was made by surgery or biopsy. Clinical diagnosis was made by the unique clinical manifestations, imaging findings, and levels of AFP and β-HCG in both serum and CSF (AFP levels greater than 25 ng/mL or β-HCG levels greater than 3 mIU/mL in blood and/or CSF were considered abnormal; normal levels, GCTs; elevated levels, NGGCTs). No tumor tissue was obtained to determine clinical diagnosis.

Clinical stages

The patients were classified as having local disease or extensive disease according to the Chang Staging System[11]. Local disease was defined as localized disease and negative CSF cytology. Extensive disease was defined as positive CSF cytology, gross nodular seeding in the cerebellar-cerebral subarachnoid space and/or spinal subarachnoid space, or extraneural metastasis.

Treatment approaches

The treatment approaches used included surgical management, radiotherapy, and chemotherapy. With radiotherapy, patients received treatment on the local tumor volume with or without whole cranial and/or whole spinal cord fields; the median dosages for local tumor volume, whole cranial, and whole spinal cord irradiation were 50.0 Gy (range, 48.0–59.0 Gy), 30.0 Gy (range, 24.0–36.0 Gy), and 30.0 Gy (range, 21.6–36.0 Gy), respectively.

Chemotherapy was primarily managed with the PEB regimen consisting of cisplatin (DDP, 20 mg/m^2, days 1–5 or 80–100 mg/m^2, day 1), etoposide (VP-16, 60–100 mg/m^2, days 1–5) or teniposide (VM-26, 60–100 mg/m^2, days 1–5), and bleomycin (BLM, 10 mg/m^2, day 1). This treatment was repeated every 3 weeks.

Response and adverse reaction assessment

The Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was used to evaluate the effect of treatment, and responses were categorized as follows: complete remission (CR), with total resolution of all imaging findings and/or tumor markers; partial response (PR), with at least 50% reduction in tumor diameter and reduced tumor marker levels if previously raised; progressive disease (PD), with more than a 25% increase in tumor diameter; and stable disease (SD), with less than 50% reduction or no more than 25% increase in tumor diameter, as well as stable or reduced tumor markers[12]. The adverse reactions were evaluated according to the National Cancer Institute Common Toxicity Criteria version 2.0 (NCI CTC v2.0).

Follow-up

All patients were followed up by blood examination and image screening every 3 months in the first year, every 6 months in the second year, and then once a year in the following years. The last follow-up visit was performed in March 2014. Survival time was calculated from the initiation of treatment to death or the last visit. For those lost to follow-up, follow-up was calculated to their last visit.

Statistical analysis

Event-free survival (EFS) was defined as the time from the initiation of treatment to first disease progression, disease recurrence,

or death from any cause. Overall survival (OS) was defined as the time from the initiation of treatment to death from any cause. Statistical analysis was carried out with SPSS 16.0. EFS and OS rates were estimated using the Kaplan-Meier method, and log-rank test was used to determine statistical significance. *P* values less than 0.05 were considered significant.

Results

Patient characteristics

A total of 57 patients were included in this study. All patients were ⩽ 18 years of age, with a median age of 12.8 years (range, 2.7 to 18.0 years) at diagnosis. Forty-one were males and 16 were females. The tumors were most commonly located in the pineal (31.6%) and suprasellar (21.1%) regions. The most common presentations were diabetes insipidus (38.6%) and intracranial hypertension (29.8%). Forty-four (77.2%) patients had localized disease and 13 (22.8%) had extensive lesions. Pathologic diagnosis was confirmed in 18 cases, of which 11 cases were germinomas; 1 case, mature teratoma; 1 case, immature teratoma; 1 case, yolk-sac tumor; 3 cases, mixed tumors; and 1 case, embryonal carcinoma. The remaining 39 patients were unable to obtain pathologic diagnosis, and they were clinically presumed to have CNS-GCTs, including 3 with germinomas and 36 with NGGCTs. Informed consent of each patient or guardian was obtained.

Of the 57 patients, 4 patients were diagnosed but not treated at our cancer center due to unknown reasons; 14 patients were diagnosed with germinomas and 39 were diagnosed with NGGCTs, and the 53 patients underwent the prescribed treatment. Here, we analyzed the treatment outcome of the 53 patients.

Treatment outcome of the patients with germinomas

Monotherapy

Four patients with localized germinomas underwent monotherapy, of which 2 underwent radiotherapy alone and achieved CR and were alive until the last follow-up. Of the 2 patients who underwent chemotherapy alone, one achieved PR and was alive until the last follow-up, and the other had PD and died of disease after giving up further treatment due to the parents' decision.

Multimodality therapies

Ten patients with germinomas, including 8 with localized germinomas and 2 with extensive lesions, underwent multimodality therapies. Five patients underwent chemotherapy plus radiotherapy, and 5 underwent complete resection plus postoperative chemotherapy and/or radiotherapy. They all achieved CR and were alive until the last follow-up.

Treatment outcome of the patients with NGGCTs

Monotherapy

Fourteen patients with NGGCTs, including 11 with localized lesions and 3 with extensive lesions, underwent monotherapy. One patient underwent surgery alone and achieved CR, but she died of relapse later. Four patients underwent radiotherapy alone, with 3 achieving CR and 1 achieving PR; 1 patient in CR died of relapse and the remaining 3 were alive until the last follow-up. Nine patients underwent chemotherapy alone, of which 2 achieved CR and 2 achieved PR, and these 4 patients were still alive until the last follow-up; 5 had PD or relapse, and they all died of disease.

Multimodality therapies

Twenty-five patients with NGGCTs, including 18 with localized NGGCTs and 7 with extensive lesions, underwent multimodality therapies. Twenty-three underwent chemotherapy plus radiotherapy, of which 17 achieved CR, 4 achieved PR, and 2 developed PD during the treatment; 3 patients in PR and 1 in CR died of relapse, whereas the other 17 in CR or PR were still alive until the last follow-up, and the 2 patients who developed PD died. Two patients underwent complete resection plus postoperative chemotherapy and/or radiotherapy, of which one achieved CR and the other achieved PR; they were both alive until the last follow-up.

Treatment outcome in patients with only a clinical diagnosis

Of the 53 patients who completed the prescribed treatment, 35 patients were clinically diagnosed with CNS-GCTs without pathologic diagnosis. Three of these 35 patients had germinomas, and 32 had NGGCTs. All the 3 patients with germinomas underwent multimodality therapies and achieved CR, with a 3-year EFS rate of 100%. Of the 32 patients with NGGCTs, 30 showed decreased levels of tumor markers in serum and/or CSF, and 29 showed reductions of tumor lesions with multimodality therapies; 22 patients achieved CR, 5 achieved PR, and 5 developed PD. The 3-year EFS rate for patients with NGGCTs was 74.2%.

Toxicities

A total of 151 cycles of PEB regimen were administered and 148 of them could be used for toxicity assessment. Grade 4 myelosuppression occurred in 15.5% of patients and grades 2–3 myelosuppression developed in 70.9% of patients. The incidence of grade 4 myelosuppresion was higher in patients with hypopituitarism than in patients with normal thyroid function (25% vs. 8.1%, P = 0.018). This condition was resolved in most patients after receiving granulocyte-stimulating factor (GSF) with or without anti-infection treatment, but 1 patient died of serious infection. Grades 2–3 gastrointestinal toxicity occurred in 49.3% of patients. Varying

degrees of radiation damage occurred in 8 patients. More specifically, 2 patients died of radiation encephalopathy, and 6 with radiation-induced hypopituitarism were required to take hormone replacement therapy to maintain normal growth and cognitive development.

Relapses

Of the 53 patients who completed treatment, 9 had relapse. Three of the 9 patients achieved a second CR after salvage and were alive at 79.0, 77.9, and 58.8 months; 6 patients had PD and died of disease after salvage therapies.

Survival

For the 53 CNS-GCT patients, the median follow-up was 32.3 months (range, 1.2 to 139 months). Fourteen patients died of disease, and 39 patients were alive until the last follow-up. The 3-year EFS and OS rates for all patients were 72.2% and 73.8%, respectively.

The 3-year EFS rates for patients who underwent monotherapy and multimodality therapies were 55.6% and 80.9%, respectively (P = 0.019; **Figure 1A**). The 3-year EFS rates for patients with germinomas and NGGCTs were 92.9% and 64.8%, respectively (P = 0.064; **Figure 1B**).

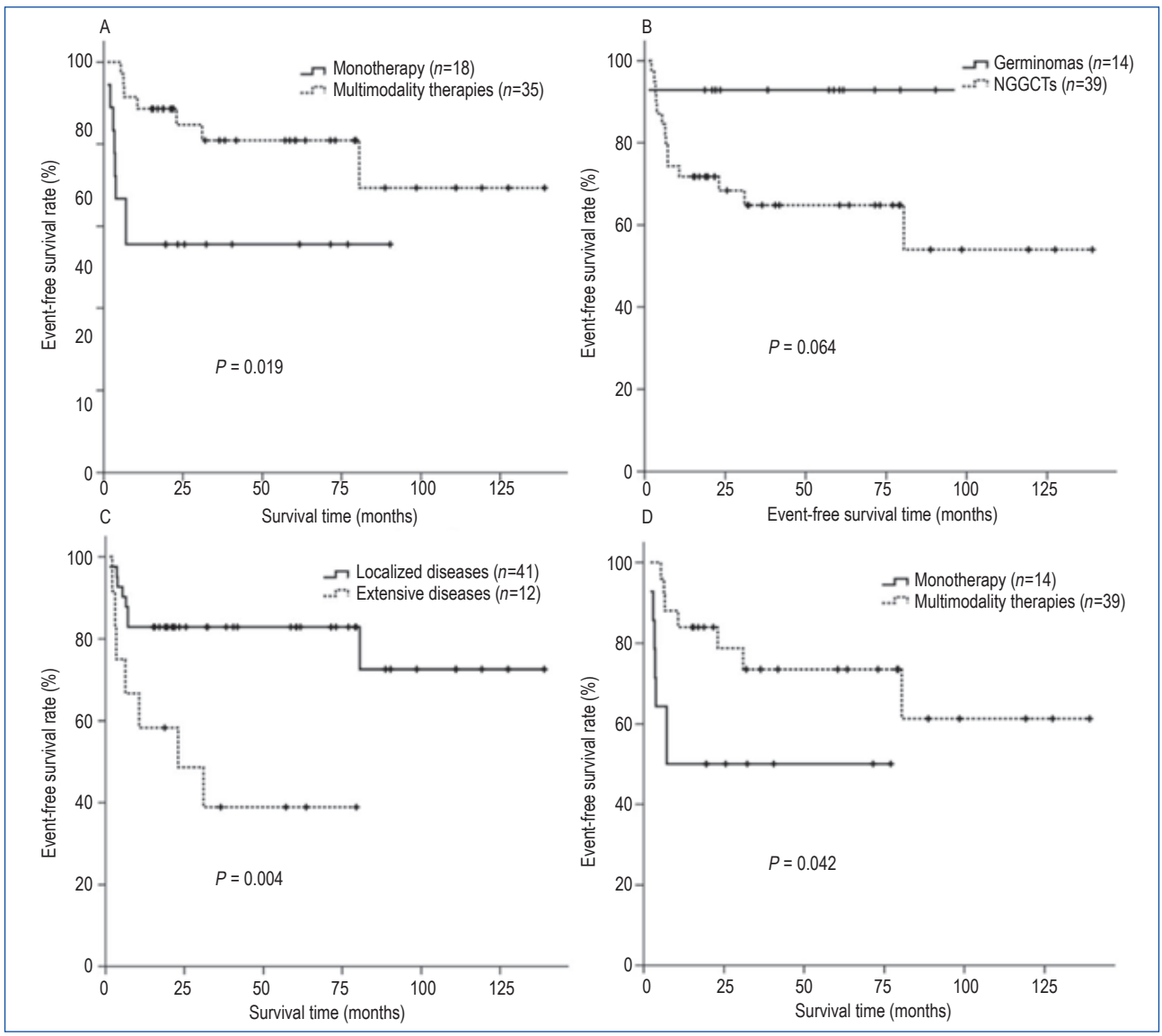

Figure 1. **Kaplan-Meier estimate of event-free survival (EFS) time for patients with central nervous system germ cell tumors (CNS-GCTs). A, the EFS curves for CNS-GCT patients with monotherapy and multimodality therapies; B, the EFS curves for germinoma and non-germinomatous germ cell tumor (NGGCT) patients; C, the EFS curves for patients with localized diseases and extensive diseases; D, the EFS curves for NGGCT patients with monotherapy and multimodality therapies.**

The 3-year EFS rates for patients with localized and extensive lesions were 82.9% and 38.9%, respectively (P = 0.004; **Figure 1C**). The 3-year EFS rates for 39 patients with NGGCTs who underwent monotherapy and multimodality therapies were 50.6% and 73.5%, respectively (P = 0.042; **Figure 1D**).

The 3-year EFS rates for patients with pathologically diagnosed NGGCTs and germinomas were 42.9% and 90.9%, respectively, whereas the 3-year EFS rates for patients with clinically diagnosed NGGCTs and germinomas were 74.2% and 100%, respectively.

Discussion

Primary CNS-GCTs occur most frequently in children and adolescents, and the incidence is significantly higher in East Asia than in western countries[1-5]. The features of our patients are similar to those in other countries[2-6]. Of the cases in our study, 24.6% were germinomas and 75.4% were NGGCTs; however, in other countries, germinomas and NGGCTs account for 55%–70% and 30%–45% of CNS-GCTs, respectively[7-10]. NGGCTs were more common than germinomas in our study. One reason was that most patients (68.4%) in our study were clinically diagnosed with CNS-GCTs according to the level of tumor markers, whereas most patients the other countries were pathologically diagnosed. Furthermore, our clinical diagnosis standards differ slightly from those of other countries, such that patients with elevated levels of β-HCG and AFP in serum and/or CSF can be diagnosed with NGGCTs. However, in other countries, AFP levels higher than 25 ng/mL and β-HCG levels higher than 50 IU/L in blood and/or CSF may indicate NGGCTs[10,12-14]. Thus, these differences may explain why germinomas were more frequent than NGGCTs in other countries.

CNS-GCTs are extremely sensitive to both radiotherapy and platinum-based chemotherapy. Most germinomas can be cured with cranial-spinal irradiation (30–36 Gy) with local boost (40–55 Gy). Such treatment has led to a cure rate of 90% for localized GCTs[15,16]. However, the long-term adverse effects of irradiation could impact growth and neuroendocrine development in children and adolescents. Reduced dosage and field irradiation combined with chemotherapy have been studied for many years. Radiotherapy and platinum-based chemotherapy for patients with germinomas have yielded 5-year OS rates of 80%–100% and 5-year EFS rates of 70%–90%[15-18]. Herein, we treated 5 localized germinomas with PEB regimen chemotherapy, followed by local boost with or without whole cranial and/or whole spinal cord radiotherapy. They all achieved CR and are all alive without recurrence. Our results were similar to those reported in other countries. Recently, in a Japanese study, localized germinomas were treated with chemotherapy combined with local volume and whole ventricular system irradiation without whole spinal cord irradiation[18]. This approach not only produced favorable survival results but also reduced the long-term adverse effects significantly[19,20]. A total of 123 patients with localized germinomas from the Japanese Germ Cell Tumor Study Group (JGCTSG) were treated with induction chemotherapy plus whole ventricular (range, 20–24 Gy) and local boost (range, 30–36 Gy) irradiation. The 5-year EFS and OS rates for these patients were both approximately 100%, and the incidence of adverse reactions resulting from radiotherapy such as hypopituitarism decreased significantly[19]. The International Society of Pediatric Oncology (SIOP) recently reported results of the SIOP CNS GCT 96 trial[21]. This prospective, multinational, nonrandomized trial for children with intracranial germinomas compared craniospinal irradiation alone with chemotherapy followed by focal primary site irradiation for patients with localized disease. Patients in group A underwent single cranial-spinal irradiation (24 Gy) and local boost irradiation (40 Gy), whereas patients in group B received 4 cycles of chemotherapy with carboplatin/VP-16 and ifosfamide/VP-16 alternately followed by local boost irradiation (40 Gy). The 5-year EFS rates of groups A and B were 94% and 88%, respectively (P = 0.72). The relapses in group B mainly occurred within the ventricular field. In general, chemotherapy followed by whole ventricular irradiation with local boost not only yielded a favorable survival but also reduced the long-term adverse effects for localized germinomas.

Clinical studies showed that patients with localized NGGCTs have a worse prognosis than do patients with localized germinomas. The 3-year OS rate was only about 40% with radiotherapy alone[13,15-18]. However, recent studies showed that chemotherapy combined with radiotherapy improved survival of patients with localized NGGCTs, with a 3-year OS rate of 60%[22-24]. Kochi *et al*.[23] reported 11 patients with localized NGGCTs who underwent platinum-based chemotherapy plus whole cranial irradiation with local boost, as well as complete resection of the residual lesions. After a median follow-up of 96 months (range, 37–177 months), the 3-year OS was 91%. Our results were similar to those from other countries above. We enrolled 39 patients with NGGCTs who had completed the prescribed treatment, and the monotherapy and multimodality therapies groups exhibited 3-year EFS rates of 50.6% and 73.5%, respectively (P < 0.05), indicating that the prognosis of NGGCTs who underwent monotherapy was poorer than that of those who had multimodality therapies. Therefore, NGGCTs should be treated with chemotherapy combined with whole cranial and spinal cord irradiation with local boost.

Primary CNS-GCTs are most commonly located in the pineal and suprasellar regions, which makes surgical excision and biopsy difficult and highly risky. Many studies classified and treated these patients according to the clinical diagnosis determined by clinical manifestations, image findings, and tumor markers[6-9]. We also adopted this diagnostic approach and treatment method. Thirty-five patients were clinically diagnosed with CNS-GCTs without pathologic diagnosis and completed all the prescribed treatment. Three of these 35 patients had germinomas and 32 had NGGCTs. All the 3 patients with germinomas achieved CR with multimodality therapies. For 32

patients with NGGCTs, the clinical manifestations showed various degrees of improvement, including 30 with decreased tumor marker levels in serum and/or CSF and 29 with reductions in tumor lesions. A total of 22 patients with NGGCTs achieved CR, 5 achieved PR, and 5 developed PD with multimodality therapies. The 3-year EFS rates for patients with pathologically diagnosed NGGCTs and germinomas were 42.9% and 90.9%, respectively, whereas the 3-year EFS rates for patients with clinically diagnosed NGGCTs and germinomas were 74.2% and 100%, respectively. They performed just as well as those who were pathologically diagnosed. These results indicated that patients who were at high risk and presented a challenge for obtaining pathologic diagnosis could be clinically diagnosed based on their clinical manifestations, image findings, and tumor markers. Thus, antitumor therapy should be carried out promptly for these patients.

Our study showed that multimodality therapies including chemotherapy combined with whole cranial and/or spinal cord radiotherapy plus local boost could significantly improve the survival rate of Chinese children and adolescents with primary CNS-GCTs.

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