ORIGINAL ARTICLE

Intracranial Germ Cell Tumors: Efficacy of Neoadjuvant Chemo-radiotherapy without Surgical Biopsy

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In this report, we review 41 patients with intracranial germ cell tumors (GCTs) treated at the Department of Neurosurgery, Keio University School of Medicine, in the 25-year period between January 1982 and July 2006. The main aim of the present study was to compare the effectiveness of our current intracranial GCT management protocol, comprising neoadjuvant chemo-radiotherapy without surgical biopsy of tumors as far as possible, to that of historical controls. In all patients, charts were reviewed and tumor and patient characteristics, including age, sex, type of tumor marker secreted, treatment protocol, and clinical outcomes, were compared. The relationship between these variables was analyzed by means of the Cox proportional hazards model. Thus far, four patients treated by approaches other than the current protocol have died of their tumor. The overall 5-, 10-, and 15-year survival rates of all the patients calculated by the Kaplan-Meier method were 91.9%, 88.6%, and 88.6%, respectively. According to the results of the Cox proportional hazards model, patients with secreting GCTs show statistically poorer prognoses than those with non-secreting GCTs ($P = 0.0073$), and although not statistically significant, patients treated with our current protocol tend to show better prognoses than historical controls ($P = 0.0543$). All five patients with secreting GCT treated using our current protocol are still alive after an average follow-up period exceeding 7 years, and only one of these has shown tumor recurrence. With our current treatment protocol comprising neoadjuvant chemo-radiotherapy without surgical biopsy, prognoses of patients with GCTs have improved compared to historical controls at our institution.   (Keio J Med 60 (2) : 56–64, June 2011)

Keywords: chemotherapy, intracranial germ cell tumors, neoadjuvant therapy, radiotherapy

Introduction

Intracranial germ cell tumors (GCTs) are not rare in Asian countries. In Japan, they account for 1.8–3.0% of all primary brain tumors and make up about 15% of all brain tumors in children.[1,2] Intracranial GCTs include several different clinical entities such as germinomas, teratomas, yolk sac tumors, choriocarcinomas, and mixed germ cell tumors.[3,4] Among these, pure germinomas can be cured by induction chemotherapy followed by reduced volume radiation therapy,[5] and mature teratomas can be cured by total tumor removal.[6] In contrast, the prognosis of patients with secreting, non-germinomatous, malignant GCTs remains poor.[3,7–9]

Human chorionic gonadotropin (hCG) and alpha-feto-protein (AFP) are considered to be powerful markers of some types of GCTs. If patients have elevated serum and/or cerebrospinal fluid (CSF) titers of these tumor markers, their tumors are considered to be secreting GCTs; in patients whose sera and CSF do not contain these tumor markers, the tumors are considered to be non-secreting GCTs. Except for teratomas, all non-germinomatous malignant GCTs are secreting GCTs.[3] Previous reports showed the efficacy of neoadjuvant therapy, comprising a combination of chemotherapy and radiotherapy followed by complete excision of residual tumors in the treatment of patients with secreting GCTs.[10,11]

In 1997, senior author K.Y. initiated a new treatment

Table 1 Data on 41 patients with intracranial germ cell tumors treated at Keio University Hospital between 1982 and 2006

	All cases	Current protocol	Others
Total cases	41	14	27
Male/female	29/12	9/5	20/7
Age at initial presentation	6–42 years	8–42 years	6–32 years
Range mean (SD)	18.46 (7.61)	17.79 (8.39)	18.81 (7.32)
Tumor location			
Suprasellar region	16	6	10
Pineal region	14	4	10
Pineal and suprasellar regions	10	4	6
Basal ganglia	1	0	1
Histological diagnosis			
Germinoma	14	2	12
Malignant teratoma	1	0	1
Germinoma with syncytiotrophoblastic giant cells	1	0	1
Mixed germ cell tumor	2 *	0	2
Diagnosis without surgical biopsy	23	12	11
Positivity for tumor markers			
AFP	3	1	2
AFP and hCG	4	2	2
hCG	8	2	6
Follow-up periods	0–229 months	14–135 months	0–229 months
Range mean (SD)	104.1 (64.2)	83.7 (41.1)	114.7 (71.9)
Number of deaths during follow-up	4	0	4

*Mixed choriocarcinoma and embryonal carcinoma, mixed germinoma and embryonal carcinoma.

protocol for intracranial GCTs at Keio University School of Medicine. According to this protocol, neoadjuvant chemo-radiotherapy is conducted without surgical biopsy of tumors as far as possible in order to prevent the frequently reported surgical dissemination of tumors.[12]

In the present study, we reviewed the treatment of intracranial GCTs at Keio University over a 25-year period. Moreover, we evaluated the efficacy of our current protocol of managing the tumors with respect to historical controls in our institution, especially in terms of secreting GCTs, which are regarded as a more malignant form of intracranial GCT.

Methods

Patient population

During the 25-year period from January 1982 to July 2006, we treated 41 patients with intracranial GCTs at the Department of Neurosurgery, Keio University School of Medicine (**Table 1**). There were 29 male patients and 12 female patients. The mean age of the patients at the time of initial presentation was 18.46 years (range, 6–42 years). Complete medical, neurological, and radiological examinations were performed in the pre- and post-treatment periods. The mean follow-up period after the initial visit

to the outpatient clinic was 104.1 months (range, 0–229 months). Before treatment, all patients underwent (1) T1-weighted magnetic resonance imaging (MRI) (with and without intravenous gadolinium infusion), T2-weighted MRI, and fluid-attenuated inversion recovery (FLAIR) MRI, and (2) computed tomography (CT) studies. If the tumor was attached to the surrounding arteries and deep veins, cerebral angiography was also performed. In all patients, the serum and/or cerebrospinal fluid (CSF) titers of hCG and AFP were evaluated. An AFP concentration of ≥ 10 ng/ml and an hCG (or hCG-β) concentration of ≥ 20 mIU/ml (milli-international units per millimeter) was defined as elevated in the present study.

Tumor location

The anatomical extent of the tumor is summarized in (**Table 1**). Sixteen (39.0%) tumors extended to the suprasellar region, 14 (34.1%) tumors were located in the pineal region, 10 (24.4%) were double tumors located both in the suprasellar region and pineal region, and 1 tumor was located in the basal ganglia.

Treatment protocol

Before 1997, when senior author K.Y. initiated the cur-

rent GCT management protocol, there was no established GCT management protocol in our institution. At that time, patients with GCTs were treated following individual ad hoc protocols consisting of surgery, chemotherapy, radiotherapy, or a combination of these.

The current treatment protocol for intracranial GCTs at Keio University is summarized in **Figure 1**. The main characteristic of our current protocol is that the tumors are diagnosed without surgical biopsy as far as possible in order to prevent surgical dissemination of tumor cells. First, presumed mature teratomas predicted by CT and MRI findings with negative tumor markers are subjected to surgery (no patient in the present study fell into this category). Other patients are basically treated without surgical biopsy as far as possible. For cases in which CT and MRI findings are not compatible with those of GCTs, we do not hesitate to conduct surgical biopsy of tumors (of the 14 patients treated by the current protocol, 2 patients were subjected to this procedure). Other patients with radiologically presumed GCTs are divided into two groups according to tumor marker secretion: the tumor marker not elevated – presumed pure germinoma group (AFP < 20 ng/ml and hCG < 10 mIU/ml, seven patients were categorized in this subgroup in the current study) and the secreting GCT group (AFP $\geq$ 20 ng/ml and/or hCG $\geq$ 10 mIU/ml, five patients were categorized in this subgroup in the current study). The treatment protocols for each clinical entity are as follows.

Presumed mature teratoma

Based on CT and MRI findings and in the absence elevated tumor markers, the tumor is presumed to be a mature teratoma. Patients undergo surgical removal of the tumor. In cases where the histological diagnosis is not in agreement with a presumed mature teratoma (e.g., it is found to be a pure germinoma), the patient is treated on the basis of the histological diagnosis.

Tumor marker not elevated, presumed pure germinoma

In the present study, seven patients were categorized in this subgroup. Patients with presumed pure germinomas undergo three courses of the chemotherapy regimen CBDCA-VP16-G (day 1: carboplatin, 450 mg/m^2; days 1–3: etoposide, 150 mg/m^2; and days 5–11: granulocyte-colony stimulating factor (G-CSF), Neutrogin, 2 µg/kg) followed by 24-Gy irradiation. In patients with localized tumors, whole-ventricle irradiation is performed. In patients with disseminated tumors, whole-brain and spine irradiation is performed additionally.

Secreting GCT

In the present study, five patients were categorized in this subgroup. Patients with secreting GCTs undergo five courses of the chemotherapy regimen ICE-G (day 1: carboplatin, 450 mg/m^2; days 2–4: etoposide, 150 mg/m^2 in combination with ifosfamide, 2 g/m^2; and days 6–12: G-CSF, Neutorgin, 2 µg/kg) followed by irradiation. For localized tumors, 24-Gy whole-ventricle irradiation was performed, and for disseminated tumors, 24-Gy whole-brain and spine irradiation in combination with 26-Gy local irradiation was performed.

Tumor marker not elevated GCTs diagnosed after surgical biopsy

When CT and MRI findings are not compatible with those of GCTs, we do not hesitate to conduct surgical biopsy. In this group of patients, when histological diagnosis of a GCT is made, we conduct intraoperative intrathecal administration of 10 mg methotrexate (MTX) to prevent surgical dissemination of the tumor. These patients undergo an adjunctive chemotherapy regimen comprising three courses of CBDCA-VP16-G with intrathecal administration of MTX, followed by 24-Gy whole-brain irradiation.

Recurrent GCTs

Patients with recurrent GCTs undergo five courses of the chemotherapy regimen ICE-G. If possible, they undergo additional irradiation. In the present study, one patient with recurrent tumor was treated by this regimen. If residual tumors are identified on follow-up MRI scans, patients undergo surgical removal of the residual tumor.

Follow-up and statistical analysis

The patients were followed up with MRI or CT imaging at approximately 6-month intervals, and the overall survival rates were calculated using the Kaplan-Meier method. The overall survival period was defined as the period from the initial presentation of the patient to our outpatient clinic (Keio University) to the last follow-up visit. To determine the factors that affect prognoses of patients, tumor and patient characteristics, including age, sex, type of tumor marker secreted, treatment protocol, and clinical outcomes, were compared. The relationship between these variables was analyzed using the Cox proportional hazards model. To compare the overall survival rates between the subgroups (i.e., secreting vs. non-secreting and treatment with the current protocol vs. treatment with other protocols), we conducted univariate analysis of possible factors by using standard log-rank
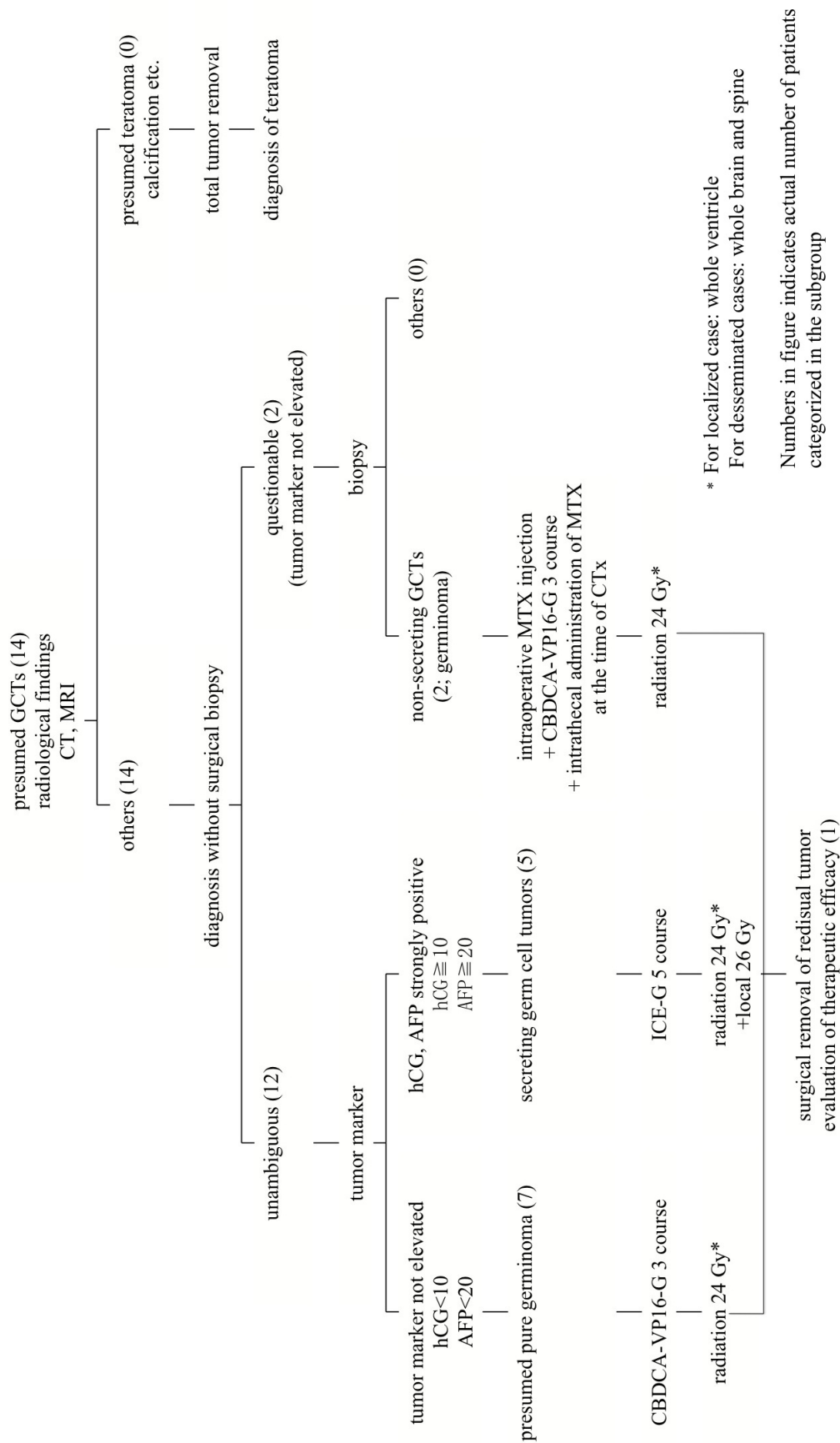
presumed GCTs (14)
radiological findings
CT, MRI

others (14)

diagnosis without surgical biopsy

unambiguous (12)

tumor marker

tumor marker not elevated
hCG<10
AFP<20

hCG, AFP strongly positive
hCG≧10
AFP≧20

presumed pure germinoma (7)

secreting germ cell tumors (5)

CBDCA-VP16-G 3 course

ICE-G 5 course

radiation 24 Gy*

radiation 24 Gy*
+local 26 Gy

surgical removal of redisual tumor
evaluation of therapeutic efficacy (1)

questionable (2)
(tumor marker not elevated)

biopsy

others (0)

non-secreting GCTs
(2; germinoma)

intraoperative MTX injection
+ CBDCA-VP16-G 3 course
+ intrathecal administration of MTX
at the time of CTx

radiation 24 Gy*

presumed teratoma (0)
calcification etc.

total tumor removal

diagnosis of teratoma

* For localized case: whole ventricle
For desseminated cases: whole brain and spine

Numbers in figure indicates actual number of patients
categorized in the subgroup

Fig. 1   Current intracranial germ cell tumor treatment protocol at Keio University (instigated in 1997).
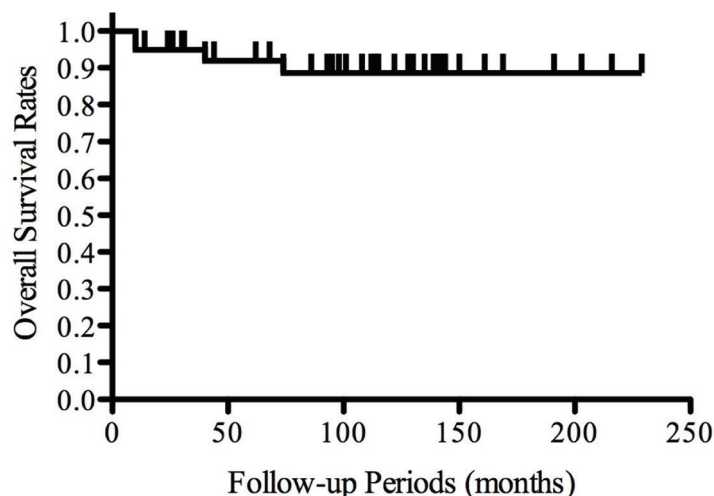
Fig. 2 Overall survival of 41 patients with intracranial germ cell tumors (Kaplan-Meier survival curve).

methods. Differences between the groups were considered to be significant at $P \leq 0.05$.

Results

Tumor markers

Serum and/or CSF titers of the tumor markers hCG and AFP were evaluated in all 41 patients. AFP alone was elevated in 3 patients, hCG alone was elevated in 8 patients, and both AFP and hCG were elevated in 4 patients. In the remaining 26 patients, serum and/or CSF titers of the tumor markers were not elevated.

Histological diagnosis of tumors

Histological diagnoses were established in 18 of 41 patients at the time before initial treatment (43.9%, **Table 1**); the diagnoses comprised 14 germinomas, 1 germinoma with syncytiotrophoblastic giant cells, 1 malignant teratoma, and 2 mixed GCTs (choriocarcinoma and embryonal carcinoma, and germinoma and embryonal carcinoma). The remaining 23 patients were treated without histological diagnoses.

Treatment protocol

Since senior author K.Y. established the new protocol in 1997, 11 patients have been treated according to the protocol. Before 1997, 3 patients were coincidentally treated with the same regimen, and we included these 3 cases in the current treatment protocol subgroup in the present study. Therefore, 14 patients were allocated to the current protocol treated subgroup. The remaining 27 patients were treated by other protocols consisting of surgery, radiotherapy, chemotherapy, or a combination of these.

Follow-up review

A review of the most recent follow-up visits (mean follow-up period, 104.1 months since the initial presentation to our outpatient clinic; range, 0–229 months) revealed that 37 of the 41 patients were still alive. Four patients treated by approaches other than by the current protocol died of the disease during the follow-up period. The Kaplan-Meier survival curve of all 41 patients is shown in **Figure 2**. The overall 5-, 10-, and 15-year survival rates were 91.9%, 88.6%, and 88.6%, respectively.

Factors that affect prognosis

To determine the factors that affect the prognoses of patients, tumor and patient characteristics, including age, sex, type of tumor marker secreted, treatment protocol, and clinical outcomes, were compared. The Cox proportional hazards model showed that among the factors evaluated, only tumor marker secretion was a statistically relevant factor that affected prognosis ($P = 0.0073$, **Table 2**). Patients treated by the current protocol tended to show longer overall survival rates than patients treated by other protocols, but the difference was not statistically significant ($P = 0.0543$). The Kaplan-Meier survival curves of patients classified by the above two factors are shown in **Figures 3** and **4**, and a summary of the p values calculated using the Cox proportional hazards model is given in **Table 2**.

The Kaplan-Meier survival curve of the 15 patients with secreting GCTs subgrouped by the treatment pro-
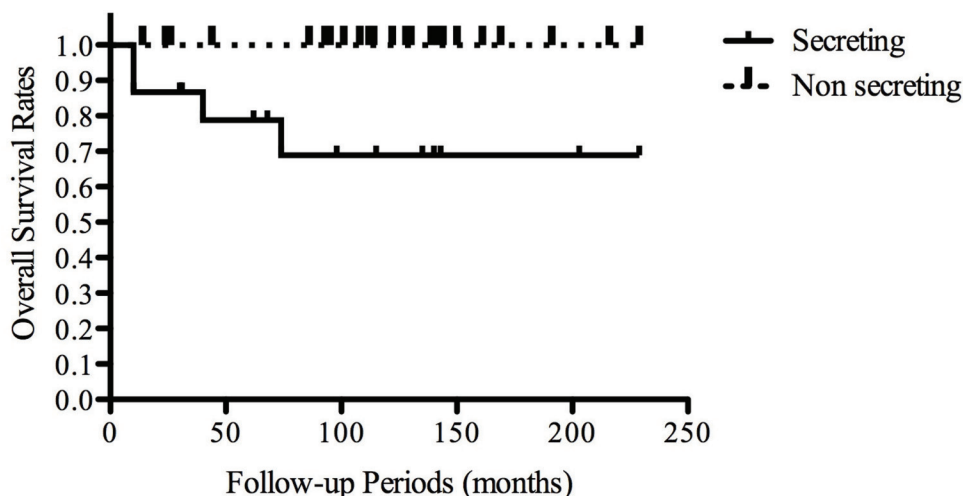
Fig. 3 Comparison of overall survival rates (Kaplan-Meier survival curve) between secreting GCTs (15 cases) and non-secreting GCTs (26 cases).
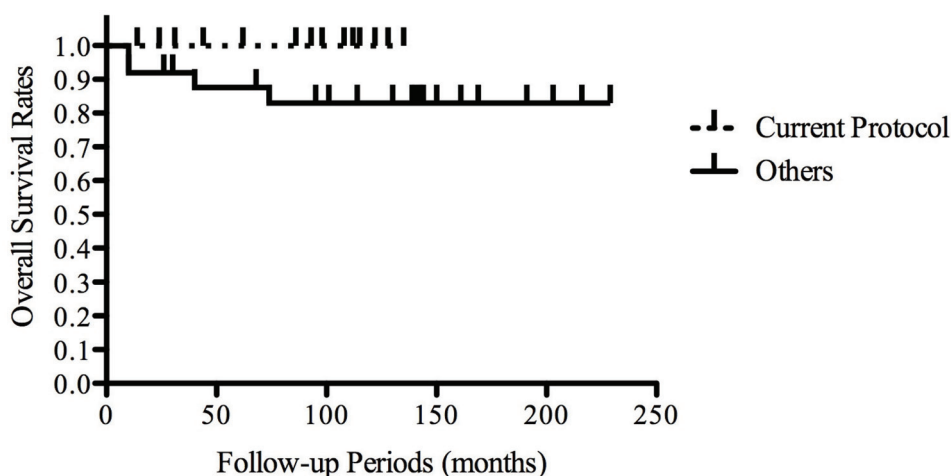
Fig. 4 Comparison of overall survival rates (Kaplan-Meier survival curve) according to treatment protocol (patients treated by the current protocol, 14; patients treated by approaches other than the current protocol, 27).

Table 2 Results of Cox proportional hazards model

Factor	P value
Age	0.3940
Sex	0.8622
Marker secretion (Yes/No)	0.0073**
Treated by current protocol (Yes/No)	0.0543

** $P \le 0.01$

tocol is shown in **Figure 5**. The characteristics of the five patients with secreting GCTs treated by the current treatment protocol are summarized in **Table 3**; only one

of them showed tumor recurrence, 10 years after initial presentation. The patient underwent additional chemo-radiotherapy for treatment of the recurrent tumor according to our current management protocol, and the tumor was controlled at 135 months from the initial presentation. The mean follow-up period of the five patients with secreting GCTs treated by the current protocol from the initial presentation is 88.2 months (range, 31–135), and all the patients are alive.

Discussion

Intracranial GCTs are malignant brain tumors that originate mainly in the suprasellar region, pineal region,
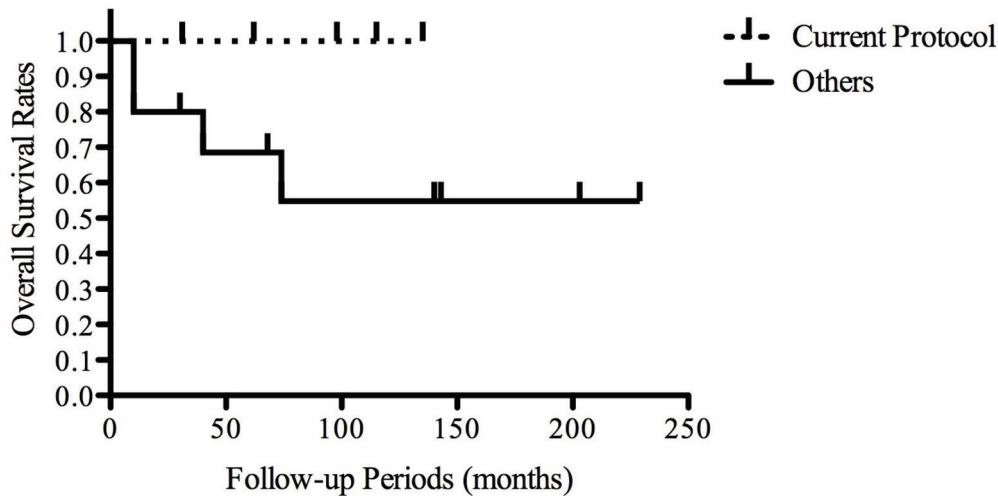
Fig. 5 Comparison of overall survival rates (Kaplan-Meier survival curve) of 15 patients with secreting GCTs according to the treatment protocol (patients treated by the current protocol, 5; patients treated by approaches other than the current protocol, 10).

Table 3 Summary of five patients with secreting GCTs treated by the current treatment protocol

Case	Age (year-old)	Sex	AFP (ng/ml)	HCG (mIU/ml)	AFP CSF (ng/ml)	HCG CSF (mIU/ml)	Follow-up period	Recurrence
1	16	M	560	86	22	24	135	Yes
2	13	M	4	36	<2	140	98	No
3	12	F	54	27	NA	NA	115	No
4	10	F	1	<1	<1	562	62	No
5	15	M	8210	1	NA	NA	31	No

M: male, F: female, NA: not available

or basal ganglia of older children and young adults.[3] GCTs encompass a number of histological subtypes, including germinomas, teratomas, embryonal carcinomas, yolk sac tumors, choriocarcinomas, and mixed GCTs.[3,4] Irradiation has been associated with a higher survival rate in patients with germinomas, but this treatment is controversial because of late side effects such as cognitive retardation and/or neuroendocrine deficiencies.[3,5] In contrast, few patients with non-germinomatous tumors (mainly secreting GCTs) survive for more than 3 years despite surgical resection in combination with radiotherapy.[3] After the success of cisplatin chemotherapy in the treatment of gonadal GCTs, intracranial GCTs were the next target of chemotherapy: the survival rates of patients with intracranial GCTs improved, but the long-term outcome of patients with intracranial GCTs, especially secreting GCTs, remains dismal.[13,14]

On the basis of these reports, Keio University (senior author K.Y.) started a new treatment protocol for the management of GCTs in 1997. Some of the features of the new treatment protocol are as follows.

1. According to the radiological findings and characteristics of the tumor markers, intracranial GCTs are divided into four subgroups: tumor markers not-elevated, presumed pure germinomas; secreting GCTs; presumed mature teratomas; and possible GCTs that need surgical biopsy for diagnosis.

2. As far possible, tumor biopsy is not used to confirm the histological diagnosis.

3. Neoadjuvant therapy comprising chemotherapy and radiotherapy is performed.

4. The dose of irradiation is suppressed to the minimum possible level.

5. If residual tumor is detected after neoadjuvant therapy, the residual tumor should be resected.

Thus far, we have treated 14 patients with intracranial GCTs with this protocol (11 since 1997).

The overall 5-, 10-, and 15-year survival rates of all 41 patients in the current study were 91.9%, 88.6%, and 88.6%, respectively. This result is similar to the reported 10-year survival rate in pure germinoma patients treated with craniospinal radiation therapy alone (around 90%).[5,15–18]

To determine the factors that affect the prognoses of patients, tumor and patient characteristics, including age, sex, type of tumor marker secreted, treatment protocol, and clinical outcomes, were compared by the Cox proportional hazards model. Of the four variables evaluated, only tumor marker secretion was shown to be a statisti-

cally significant factor that affected prognosis. Patients with non-secreting GCTs tended to live longer than those with secreting GCTs, as reported previously.[3] Patients treated with the current protocol tended to live longer than those treated by other protocols; however, the difference was not statistically significant ($P = 0.0543$). In the current series, only four patients died of the tumor; this is probably one of the reasons why the current results were not statistically significant. We believe that a longer-term study with a larger sample size is required to prove the possible efficacy of our current protocol statistically. We should mention that the current protocol is a uniform protocol, as described above; however, other protocols consist of ad-hoc approaches. Consequently, the difference between the survival periods in patients treated with the current protocol and in patients treated with ad-hoc protocols indicates the benefit of a uniform therapy along with the current protocol over ad-hoc protocols including outdated approaches.

The efficacy of our current protocol compared to historical controls at our institution is especially evident with regard to the overall survival rates of patients with secreting GCTs. Even thought the results were not statistically significant by a log-rank test ($P = 0.1338$), patients in this subgroup treated with the current protocol tended to live longer than those treated with other protocols. In the present study, the overall 5-year survival rate of patients with secreting GCTs treated by the current protocol was 100%. According to previous reports, the median length of survival in this subgroup is less than 2 years, and fewer than 30% live as long as 5 years after initial diagnosis.[7–9] Robertson, et al.[19] reported a better 4-year overall survival rate: it was 74% in secreting GCT patients treated with multimodality therapy. In the present series, we followed up five patients with secreting GCTs treated with our current management protocol for an average of more than 7 years (88.2 months) since initial presentation, and all the patients are still alive. Although only five of our patients were in this subgroup, we believe that the outcome of this new management protocol is at least comparable to that of previous reports, and that it can ensure longer survival of patients with intracranial secreting GCTs. As for patients with tumor marker not-elevated presumed pure germinomas or histologically confirmed germinomas, no death was observed during the study periods irrespective of treatment protocols. So our suggested new current protocol seems especially effective in patients with secreting GCTs, which is thought to be more malignant in nature.

As for neoadjuvant chemotherapy for secreting GCTs, in 1994, Herrmann, et al. reported the cases of three secreting intracranial GCT patients who underwent neoadjuvant chemotherapy and reported the effect of preoperative chemotherapy in terms of reduction of tumor volume and normalization of tumor markers.[12] In 1999 and 2003, Ushio, Kochi, and colleagues reported that they administered neoadjuvant chemo-radiotherapy to 11 patients with secreting GCTs. They performed surgical biopsy of the tumor before treatment in five cases in which histological diagnosis without the tumor marker was controversial. It is noteworthy that they administered neoadjuvant chemo-radiotherapy without surgical biopsy of the tumor in six cases. They concluded that neoadjuvant therapy, consisting of combined chemo-radiotherapy, followed by complete excision of residual tumors is highly effective in patients with intracranial secreting GCTs.[10,11]

Before administration of chemo-radiotherapy, tumor biopsy is usually performed at other hospital to obtain a histological diagnosis of presumed intracranial GCTs that arise in the suprasellar region, pineal region, and/or basal ganglia.[12] However, most intracranial GCTs have mixed histological characteristics, and treatment is successful only when the most malignant component of the tumor is targeted. Therefore, a biopsy specimen obtained by surgical biopsy is not always representative of the complex histological characteristics of tumors and may sometimes have limited value in terms of diagnosis.[20,21] Furthermore, it is known that surgery, even a stereotactic biopsy of GCTs, can cause dissemination of tumor cells into the CSF and lead to metastases along the ventricular wall or within the subarachnoid space.[12] According to our new protocol, instead of classifying GCTs on the basis of histological diagnosis of the surgical biopsy specimen, we attempt to classify intracranial GCTs according to the characteristics of the tumor markers and radiological findings into four subgroups: (1) presumed pure germinoma, (2) secreting GCT, (3) teratoma, and (4) possible GCTs that need surgical biopsy for diagnosis. We administer neoadjuvant chemo-radiotherapy without surgical biopsy to patients in subgroups (1) and (2). Surgical dissemination of GCTs has been reported previously; we therefore think that the use of neoadjuvant chemo-radiotherapy without surgical biopsy, especially in the case of patients who show marked elevation in the levels of tumor markers, is justified.[22,23] In addition, one case of extraneural metastasis of intracranial GCT[24] and one of GCT arising from multiple sites of the body[25] have also been reported. Multimodal therapy allows long-term survival of patients with intracranial GCTs. We believe that neoadjuvant therapy without surgical biopsy of tumors could have an effect on preventing tumor relapse.

Our current treatment protocol, i.e., neoadjuvant chemo-radiotherapy without surgical biopsy as far as possible followed by residual tumor resection, has been routinely conducted since 1997. Follow-up results revealed that with this current protocol, patients with intracranial GCTs tend to live longer compared to historical controls at our institution. A noteworthy result was that all five patients with secreting GCTs treated with this protocol survived, with an average follow-up period of more than 7 years. With our current treatment protocol comprising neoadjuvant chemo-radiotherapy without surgical biopsy, prognoses of patients with GCTs have improved com-

pared to historical controls at our institution.

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