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Original Paper

Germ Cell Tumours of the Central Nervous System: Treatment Consideration Based on 111 Cases and their Long-term Clinical Outcomes

Y. Sawamura,[1] J. Ikeda,[1] H. Shirato,[2] M. Tada[1] and H. Abe[1]

Departments of [1]Neurosurgery and [2]Radiology, Hokkaido University School of Medicine, North 15, West 7, Kita-ku, Sapporo, 060 Japan

Germ cell tumours (GCTs) of the central nervous system (CNS) encompass various histological subtypes, and their optimal management has been the subject of debate. To indicate a better management strategy for each subtype, we analysed the records of 111 patients (median age 14 years), who underwent treatment since 1970. With a median follow-up duration of 86 months, the probability of surviving 5 years was: 96% for pure germinoma patients, 100% for mature teratoma, 67% for immature teratoma and 69% immature teratoma mixed with germinoma. The probability of cause-specific progression of germinomas producing human chorionic gonadotropin (HCG) was higher than that of non-producing germinomas ($P < 0.01$). GCTs that included a highly malignant component, such as embryonal carcinoma or yolk sac tumour, exhibited a poor prognosis with 38% chance of 5-year survival. Late adverse effects of therapy included stroke, secondary malignancy and cognitive, endocrinological, auditory and visual dysfunctions. Of 85 survivors with a median follow-up period of 99 months, 58 patients needed hormone replacement therapy, 26 patients showed poor performance status and, to date, only 1 patient has fathered children. Because the outcomes varied widely for each subtype, the traditional categories, that is, germinoma and non-germinomatous GCT as an extrapolation from the gonadal GCTs, are not suitable for appropriately selecting therapeutic regimen for CNS GCTs. © **1998 Published by Elsevier Science Ltd.**

Key words: central nervous system, germ cell tumour, germinoma, radiation therapy, treatment outcome
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INTRODUCTION

IN CONTRAST to gonadal germ cell tumours (GCTs), primary GCTs of the central nervous system (CNS) are a rare neoplasm of children and young adults: annually only 30–40 new cases are expected to occur in children in the U.S.A. [1] and probably not more than 10–20 cases per year in the U.K. [2]. In the Western hemisphere, this amounts to no more than 2% of all primary intracranial malignancies in patients under 20 years of age [3]. These GCTs are, however, more common in far-east Asia—the incidences in the U.S.A. and Japan account for 0.5% and 3.1% of all primary brain tumours, respectively [4, 5].

The category 'germ cell tumour' encompasses a number of histological subcategories [6], with diverse treatment responses which show similar clinical manifestations and radiological features [7–10]. Adequate survival has been reported for patients with CNS germinoma, treated only with large-volume radiotherapy [8, 9, 11–16]. In contrast, more malignant CNS GCTs, such as embryonal carcinoma, yolk sac tumour, immature teratoma, teratoma with malignant transformation or mixed GCTs, generally show poorer survival rates [9, 12, 13, 15, 17–21]. The best treatment for each of these subtypes in the CNS is still to be defined. Furthermore, because of the anatomical and functional complexity of the CNS, outcome appears to depend on the location and extent of the tumour [9, 13, 16, 22, 23]. Although a greater resection is associated with a higher rate of survival for non-germinomatous GCT [24], an aggressive surgical approach has been advocated only for pineal region tumours, but not for hypothalamic/neurohypophyseal tumours [22, 25]. Thus, the selection process for the appropriate treatment of CNS GCTs is complex.

Each subcategory of CNS GCT includes uncommon neoplasms. The vast majority of these have been described in case reports or as small series in the literature [9]. Although

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some review articles have addressed the natural history, management plans and treatment outcomes of the different histological subtypes, relatively rare types of GCT have not received as much attention, particularly with regard to management and treatment selection [8, 9, 12, 13, 15].

In order to indicate suitable treatment for each subcategory of GCT, we retrospectively assessed survival rates, recurrence rates and functional outcome resulting from radiation-based treatment in 111 patients. In addition, we present late adverse effects of adjuvant therapy on the CNS in young patients.

PATIENTS AND METHODS

Clinical materials

The records of 111 patients with primary CNS GCT treated in the Hokkaido University Hospital and its affiliated hospitals between 1970 and 1995 were retrospectively analysed (Table 1). The median age at the initiation of treatment was 14 years old (range 2–37 years) and the subject group included only 4 young children below the age of 5 years (Figure 1).

The analyses were performed according to revised World Health Organization histological classification (Table 2) [6]. In this analysis, 'GCTs with highly malignant component' included teratomas with malignant transformation, embryonal carcinoma, or yolk sac tumour. No choriocarcinoma was observed. Teratomas with malignant transformation contained a malignant component such as adenocarcinoma, squamous cell carcinoma or mesenchymal carcinoma.

Of the 74 patients with germinoma, 14 showed elevated serum levels (range 5–200 mIU/ml) of human chorionic gonadotropin (HCG). In this report, such tumours are referred to as 'HCG-producing germinoma'. There were 24 histologically unverified germinomas. Unverified germinoma was defined as such if it met the following clinical criteria: less than 20 years of age and presenting *diabetes insipidus* or Parinaud's sign as an initial manifestation. Radiological criteria were: involvement of both the pineal and suprasellar regions for multifocal germinoma; invasion to the bilateral posterior thalamus for solitary pineal germinoma; involvement of the neurohypophysis for solitary suprasellar germinoma. Additionally, these tumours had to display high radiosensitivity exemplified by remarkable tumour shrinkage after 10–20 Gy irradiation and disappearing completely after the conclusion of radiotherapy. Of the 24 cases, there were 18 tumours involving the neurohypophyseal region and another 6 occurring as solitary pineal mass.

Table 1. *Summary of* 111 *patients with intracranial germ cell tumours*

	No. (unless otherwise stated)
Total number of patients	111
Median age (years)	14 (range 2–37)
Male/female	91/20
Location of tumours	
Solitary pineal	37
Solitary neurohypophyseal/hypothalamic	45
Solitary at other sites	2
Multifocal	22
Dissemination	5
Radiation therapy (total 105 cases)	
Field	
Craniospinal	17
Whole brain or ventricle	51
Localised	37
Total tumour doses (mean±S.D.)	
Germinomas	40.6 ± 9.0 Gy
Non-germinomas	46.6 ± 8.5 Gy
Chemotherapy (total 36 cases)	
Germinomas	24
Non-germinomas	12
Median follow-up period after treatment	86 months

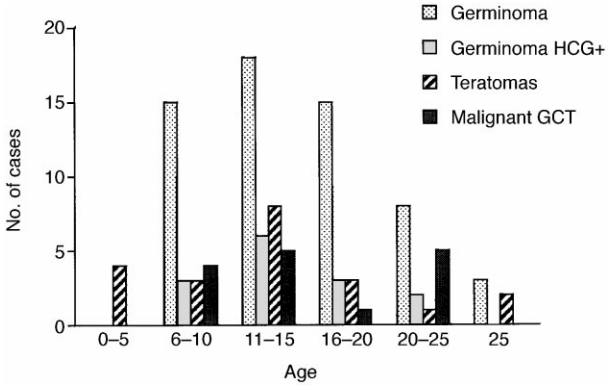

Figure 1. Distribution of cases by age and histology.

Table 1 shows tumour locations at diagnosis. Only 1 of the 37 patients with a solitary pineal lesion was female. The other 19 female patients had neurohypophyseal/hypothalamic lesions.

Radiation therapy

The treatment plan changed over the 25 years. Empirical radiation therapy was utilised for patients with suspicious germinoma throughout the 1970s, due to the conspicuous radiation sensitivity of germinoma and the then high neurosurgical morbidity [16, 26, 27]. Between 1980 and 1990, pineal germinomas were surgically resected, but germinomas in the other regions were first treated by empirical radiation. After 1990, all germinomas, including hypothalamic–neurohypophyseal lesions, were to be histologically verified by surgery before chemoradiation therapy. Throughout the study period, non-germinomatous GCTs, including tumours which were resistant to empirical irradiation, had been subjected to surgical removal before adjuvant therapy.

Radiation therapy was given to all but 6 patients. Of the 6 patients who did not receive radiotherapy, 3 patients had mature teratoma which were totally resected and 3 patients died of radical surgery. Various radiation doses and treatment fields were used, according to both treatment policy and on prognostic factors at the time. Before 1990, patients with a solitary germinoma received 35–50 Gy of whole brain or whole ventricle irradiation and patients with multifocal germinoma or disseminated germinoma were treated with craniospinal irradiation with approximately 45 Gy of local tumour dose. Irradiation was fractionated four times a week and the daily dose was 2.0 Gy for the majority of patients. However, some patients were treated with 2.5 Gy in the 1970s. The median dose for craniospinal irradiation was 30 Gy, using a daily dose of 2.0 Gy. A smaller dose of less than 2 Gy four times a week was not available in our institute due to practical limitations.

Table 2. The 1-, 5 and 10-year survival rates for each patient group with various histological subcategories

	No. of cases	Median follow-up period (months)	Survival rates (%)		
			1-year	5-year	10-year
Germinomas	74	100	99	93	84
Pure germinoma	60	101	98	96	90
(Histologically verified)	36	68	97	93	88
(Univerified)	24	154	100	100	94
HCG-producing germinoma	14	81	100	82	60
Teratomas	22	74	82	77	77
Mature	6	121	100	100	100
Immature	9	36	67	67	67
Mixed with germinoma	7	60	86	69	69
GCTs with a highly malignant component*	15	30	73	38	25
Teratoma with malignant transformation	4	14	75	50	50
Embryonal carcinoma mixed with immature teratoma	7	34	71	43	43
Yolk sac tumour	4	14	75	25	0
All cases	111	86	92	83	75

*Germ cell tumours including certain types of cancer tissue, such as embryonal carcinoma, adenocarcinoma, mesenchymal carcinoma, or squamous cell carcinoma. HCG, human chorionic gonadotropin; GCT, germ cell tumour.

Since 1991, all patients with germinomas were first treated with preradiation chemotherapy and then received 24 Gy of localised irradiation, but only patients with disseminated germinoma were given 24 Gy of craniospinal irradiation. Patients with non-germinomatous GCT were generally treated with craniospinal irradiation and a total tumour dose of approximately 40–60 Gy. Since 1991, those patients with non-germinomatous GCT, except for mature teratoma, also received chemotherapy in combination with concurrent radiation therapy. The dosage for craniospinal irradiation was 24 Gy/12 fractions/4 weeks.

Chemotherapy

The treatment plan for chemotherapy also changed over the 25 years. Between 1970 and 1990, chemotherapy was not included as part of the initial therapy, but was given to patients with recurrent disease. Various modes of salvage chemotherapy were used in 14 patients with recurrent disease (8 germinomas and 6 non-germinomatous GCTs). The agents used were: cisplatin, carboplatin, vincristine, bleomycin, methotrexate, etoposide and ifosfamide. Since 1991, all 22 patients (16 germinomas and 6 non-germinomatous GCT) received chemotherapy after surgical removal or biopsy. In this later period, 6 patients with solitary pure germinoma were given a combination of cisplatin and etoposide and 10 patients with multifocal or disseminated germinoma were treated with pre-irradiation chemotherapy of cisplatin, etoposide and ifosfamide. Following chemotherapy, these germinoma patients received 24 Gy of local irradiation. 6 patients with non-germinomatous GCT were given combination chemotherapy of cisplatin, etoposide and ifosfamide with concomitant radiation therapy.

With the advent of computerised topography (CT), patients underwent CT or MRI (magnetic resonance imaging) study approximately once a year at least for several years after treatment and thereafter only as clinically indicated. Routine neurological examination was carried out in all patients, but an exact neuropsychological testing was only performed as clinically indicated, although since 1992 all patients had to be examined. Almost all patients received endocrinological examinations after treatment.

Survival curves were calculated using the Kaplan–Meier method because of the small number in each group. Survival was defined from the commencement of treatment to death or last follow-up visit. Progression-free survival was defined as the interval from the commencement of treatment to relapse, progression, or last follow-up evaluation. Univariate analysis for survival was carried out using the Cox–Mantel test and the generalised Wilcoxon test.

RESULTS

Survival

When the analyses were performed in July 1997, 85 patients were alive and 26 patients deceased. The life table analysis according to Kaplan–Meier (Figure 2 and Table 2) shows survival rates with a median follow-up of 86 months. Figure 3 presents the cause-specific progression.

Half the patients with GCT with a highly malignant component died of disease in the first 2 years, while some patients with germinoma died of late recurrence, years after the initial treatment. When the GCTs were divided into four groups—pure germinoma, HCG-negative ($n = 60$), human chorionic gonadotropin (HCG)-producing germinoma ($n = 14$), teratomas ($n = 22$), and germ cell tumour (GCT) with a highly malignant component ($n = 37$) (Figure 2),—the differences were not statistically significant by the generalised Wilcoxon test, but some were significant by the Cox–Mantel test (pure germinoma versus HCG-germinoma, $P < 0.01$; pure germinoma versus teratoma, $P < 0.05$; pure germinoma versus GCT with a malignant component, $P < 0.01$; teratoma versus GCT with a malignant component, $P < 0.05$).

There were 4 deaths directly related to radical surgery, so the operative mortality was 3.6%. Ninety-eight per cent of patients achieved remission at least 3 months after initial surgery, radiotherapy and chemotherapy, whilst 13 patients failed. The probabilities of cause-specific progression at 5 years and 10 years were 0.20 and 0.20 for pure germinomas, 0.24 and 0.72 for HCG-producing germinomas, 0.52 and

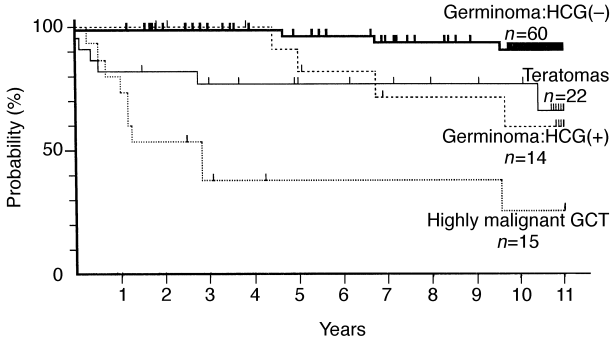

Figure 2. Overall survival from the date of treatment for all 111 patients with pure germinoma, with human chorionic gonadotropin (HCG)-producing germinoma, with teratomas, or with germ cell tumour (GCT) with a highly malignant component. Teratomas include mature teratoma, immature teratoma and mixed germ cell tumour (teratoma mixed with germinoma). The tick mark indicates last follow-up.

0.52 for immature teratomas and 0.60 and 0.87 for GCTs with a highly malignant component, respectively. None of the mature teratomas recurred. The difference between pure germinoma versus HCG-germinoma was statistically significant ($P < 0.01$; Cox–Mantel test). The median time to tumour progression was 23 months in pure germinomas, 63 months in HCG-producing germinomas, 4 months in immature teratomas and 10 months in GCTs with a highly malignant component, respectively. Salvage therapy appeared to be effective for recurrent pure germinomas, HCG-producing germinomas and immature teratomas, but not for GCT with a highly malignant component (Figures 2 and 3, Table 2).

Performance status in 85 *survivors*

A total of 85 survivors were reviewed at a median follow-up period of 99 (range 6–313) months after treatment. 65 of 74 germinoma patients and 20 of 37 non-germinomatous GCT patients had survived to the final observation point. Table 3 summarises Karnofsky's performance status and the use of hormone replacement therapy.

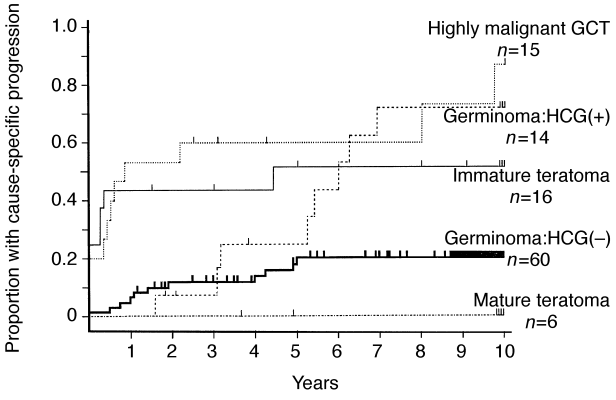

Figure 3. Cause-specific progression for all 111 patients with pure germinoma, with human chorionic gonadotropin (HCG)-producing germinoma, with mature teratoma, immature teratoma, or with germ cell tumour (GCT) with a highly malignant component. Immature teratoma includes mixed germ cell tumour (teratoma mixed with germinoma). The tick mark indicates last follow-up.

Only 11 (13%) of the 85 patients had no physical or neurological deficits with 100% performance status. Physical or cognitive sequelae, or both, were present in 87% (74/85) of patients, with 31% (26/85) showing low performance-status levels of less than 80%.

The 48 patients who showed 80–90% performance status were nearly fully active in daily life. In this population, deficits were mainly due to endocrinological, visual, or both problems. Among the 26 patients who showed less than 80% performance status, the majority suffered from cognitive dysfunctions and some had severe motor paresis or visual disturbance. Of them, 9 patients showed prominent postsurgical worsening of performance status. The overall surgical morbidity observed in survivors was 19% (16/85), including minor neurological deficits, such as upward gaze palsy or visual field defects. 7 patients had late delayed deterioration, which was considered to be related to radiation therapy, although in 2 patients with recurrent germinoma, an effect of salvage cisplatin-based chemotherapy could not be ruled out.

High-tone hearing loss was observed in 32 patients treated with cisplatin, although it was very mild due to a careful otological monitoring during therapy and did not impair these patients' daily life. Among 85 survivors, 5 patients, who did not receive chemotherapy, needed a hearing aid due to late-onset hearing loss attributed to whole brain or craniospinal irradiation. Post-treatment deterioration of visual function, without evidence of tumour progression, occurred in 2 patients who had moderate visual disturbance at onset and had received radiation therapy involving the suprasellar region. They were visually handicapped with a visual acuity worse than 'discrimination of in-front hand movement'. Persistent adverse effects of chemotherapy on patients with recurrence was not clear as most of the patients who received salvage chemotherapy with or without re-irradiation died. Since 1991, 22 patients had received chemotherapy as an initial therapy, and 21 did not suffer from any persistent or late adverse effects of the chemotherapy, with one patient having mild high-tone hearing loss due to cisplatin. A 24-year-old

Table 3. *Performance status and requirement of hormone replacement therapy in* 85 *survivors at the median follow-up period of* 99 *months*

Karnofsky performance status (%)	Number of patients		
	Total ($n = 85$)	Germinomas ($n = 65$)	Non-germinomas ($n = 20$)
100	11	7	4
90	26	20	6
80	22	17	5
70	11	8	3
60	11	9	2
50	1	1	0
40	3	3	0
Hormone replacement therapy			
Neurohypophyseal lesion ($n = 54$)			
Yes	53 (98%)		
No	1 (2%)		
No neurohypophyseal lesion ($n = 31$)			
Yes	5 (16%)		
No	26 (84%)		

male patient with a solitary hypothalamic mixed germ cell tumour, including embryonal carcinoma, presented transient brain-stem encephalopathy involving the medulla oblongata which caused moderate hemiparesis. This occurred 2 years after the initial chemoradiation therapy composed of 24 Gy craniospinal and 30 Gy local (hypothalamic region) irradiation and combination chemotherapy of cisplatin (total dose; 600 mg/m^2), etoposide (1.8 g/m^2) and ifosfamide (24 g/m^2).

Requirement of hormone replacement therapy

Irrespective of the initial manifestation, all patients with a neurohypophyseal lesion had hormone deficiencies, such as *diabetes insipidus* or anterior pituitary dysfunction. Hormone replacement therapy was necessary for 68% (58/85) of the long-term survivors. Among 30 patients without any evidence of disease in the hypothalamic–pituitary axis, 5 (16%) patients, all of whom had a solitary pineal tumour, required replacement therapy due to late-onset pituitary dysfunction. Because these 5 patients were not given chemotherapy, this side-effect was probably related to radiation therapy, which was more than 35 Gy covering the hypothalamic–pituitary axis.

58 patients reached 20 years of age, 41 with pituitary dysfunction. Gonadotropin replacement was administered to certain patients with pituitary–hypothalamic hypogonadism. 5 patients married after treatment for tumour, but only 1 male patient was able to father children. This patient received 47.5 Gy of localised irradiation for multiple germinoma in the pineal and neurohypophyseal regions at 15 years and had had only *diabetes insipidus* after therapy.

Cerebral atrophy and necrosis

Possible radiation damage to the brain parenchyma was found on CT or MRI in 19 patients, all of whom received large volume irradiation. Generalised brain atrophy was notable in 14 patients, multicystic cerebral malacia was found in 3 patients and focal radiation necrosis occurred in 2 patients; for these 19 patients, the median age was 13 years at the time of radiation therapy.

Although the patients were not constantly monitored by neuropsychological examination, 7 of the 19 showed various degrees of mental retardation or deterioration, exhibiting intelligence quotients ranging from 65 to 83, which hampered their social activity. The other 12 patients did not show any remarkable neurocognitive deterioration or retardation.

13 of 14 patients in whom generalised brain atrophy was seen had been treated before 1991. After 1991, the mode of radiation therapy was modified as mentioned above. Of 14 patients, 5 were given whole ventricle or more wide-field irradiation of more than 35 Gy with 2.5 Gy of daily fraction, and the others received 2 Gy per day. 7 of the 14 patients treated were under 10 years of age.

Radiation necrosis of the medulla oblongata occurred only in 2 patients who had recurrent germinoma; one was lethal and the other resulted in tetraparesis. An excess of secondary radiotherapy for the recurrence was responsible for their necrosis. 2 of 3 young patients with multicystic encephalomalacia received both cisplatin-based chemotherapy and irradiation. The patients were given irradiation covering the whole ventricle field and a combination chemotherapy of cisplatin, vincristine and bleomycin following the radiotherapy. Their leucoencephalomalacia had progressed continuously for several years.

Secondary neoplasms

Radiation-induced neoplasms occurred in 4 patients; two glioblastomas and two meningiomas. The patients were initially treated with wide-field radiation therapy, but not chemotherapy and had been free from recurrence for a considerable period before the secondary tumour appeared.

A 14-year-old boy with a solitary pineal germinoma was treated with 30 Gy craniospinal irradiation and a 15 Gy local boost. Twelve years later, at the age of 26 years, he developed a glioblastoma and died shortly afterwards. Another patient, a 6-year-old girl with neurohypophyseal immature teratoma and elevated levels of serum HCG, was treated with 30 Gy whole ventricle field irradiation and a 20 Gy local boost. Ten years later, she developed a glioblastoma in the right temporal lobe and died of the tumour. A 10-year-old boy with neurohypophyseal germinoma developed a frontal falx meningioma 15 years after radiation therapy and a 12-year-old boy with a pineal germinoma developed a petroclival meningioma 19 years after treatment.

A total of 84 patients survived longer than 2 years after radiation therapy. Their mean age was 14.4 years and the median follow-up period was 115 months, ranging from 25 to 313 months after irradiation. Because postradiation neoplasms generally occur years after initial therapy, the incidence of radiation-induced neoplasm was 4.8% (4/84) when calculated in this population. The incidence of secondary neoplasms over 19 years was estimated to be 16.8% (95% confidence interval, 8.1–25.5%). The incidence of radiation-induced neoplasms may continue to increase with longer follow-up.

Cerebral artery occlusions

Radiation-induced occlusive vasculopathy of large intracranial arteries occurred in 3 patients. They were irradiated over the parasellar region at 6, 14 and 16 years of age. All the affected arteries were included in the radiation field. 2 patients had a stroke, 2 and 14 years after irradiation, after which both patients remained moderately hemiparetic. When ischaemic stroke occurred, these young patients were tumour free and had no risk factors, such as hypertension, hyperlipidaemia or atherosclerosis of other major cerebral arteries. A huge dural arteriovenous malformation developed in another patient 11 years after irradiation, although it was asymptomatic. The incidence of stroke over 16 years was estimated to be 11.7% (95% confidence interval, 5.5–18.0%).

DISCUSSION

No significant difference in survival rates was observed among each subtype of GCTs, owing to the small numbers of patients, but, our survival rates were similar to those results reported by Sano [15]. Sano's series, which analysed the long-term outcome of 119 cases, is one of the largest series to date on CNS GCT. According to his results, patients with germinoma had 5- and 10-year survival rates of 95 and 91%, respectively, patients with mature teratoma had a 5-year survival rate of 93%, patients with immature and malignant teratoma had a 5-year survival rate of 75% and cases of yolk sac tumour, embryonal carcinoma and choriocarcinoma had poor outcomes, with a 5-year survival rate of less than 45%.

In our series, for pure germinomas, the probability of surviving 10 years was 90%, whilst the progression-free survival rate was 80% with a median follow-up period of 101 months.

Both rates were 100% for mature teratoma. Calaminus and colleagues reported that event-free survival was 90% with a median follow-up of 20 months for patients who received only radiotherapy, which was craniospinal irradiation in most of the cases [12]. In the Maligne Keimzelltumoren trials, 32 patients with CNS germinomas and receiving craniospinal irradiation with a tumour boost achieved a 91% event-free survival rate, with a median survival time of 55 months [28]. Another recent review reported on the treatment of 24 germinomas by irradiation alone at the University of California in San Francisco [29]—at 5 years, the disease-free survival rate was 91%. With regard to survival rates only, these and our results strongly suggested that cure rates better than, or around, 90% should be achievable in any future therapeutic trials for CNS germinoma and mature teratoma.

Our study showed that physical or cognitive sequelae, or a combination of both, occurred in 72 of 85 survivors. Although most children displayed endocrine and/or cognitive deficiencies at the onset of disease, plausibly reflecting the original tumour site, the radiation dose/volume which was administered to patients before 1991 was considered to be sufficient to cause a deterioration. It has been reported that, while the chances of survival for patients with CNS germinoma are excellent, the conventional radiation therapy, as we had previously applied, carries significant risks of neurological sequelae in young patients [8, 14, 16, 19]. In this population, a major goal should be the reduction of post-treatment sequelae and the preservation of neurocognitive and endocrinological functions. Determining the minimum volume of effective radiation for germinoma is currently the main issue [16, 30].

An international co-operative therapeutic trial was recently undertaken to determine whether irradiation could be avoided [3]. The study utilised combination chemotherapy for 45 patients with CNS germinoma. At a median follow-up duration of 31 months, relapse or progression occurred in 22 patients and 7 patients died. The results of this study are encouraging and suggests that chemotherapy alone can be an alternative curative therapy. However, the use of reduced-volume of radiotherapy may be currently indispensable. Allen and associates [11] used carboplatin to treat 11 patients with germinoma and then added a reduced dose of irradiation: 30 Gy to the involved field and 21 Gy to the craniospinal axis. 10 out of 11 patients (91%) remained in continuous remission for a median of 25 months. In the TC 90 protocol of the SFOP (French Society of Paediatric Oncology) [12], the agents, carboplatin, etoposide and ifosfamide, were used before local irradiation of 40 Gy. Patients treated with this protocol achieved approximately 92% event-free survival with a median follow-up of 10 months. Although the observation periods are short and germinomas may recur years after treatment, as found in our study, this pre-irradiation chemotherapy in combination with reduced doses or volume of irradiation is attractive.

Generally, impaired pituitary functions before treatment persist or worsen after remission [32]. Pituitary hormone replacement therapy was required for 68% of patients in this series. Furthermore, among 31 patients without any evidence of disease in the hypothalamic–pituitary axis before treatment, 5 patients required replacement therapy, which is considered as late-onset pituitary dysfunction. To avoid this, a reduced-radiation dose covering the hypothalamic–pituitary unit may be recommended if disease control could be achieved. Currently, we have been treating patients with CNS germinoma with pre-irradiation chemotherapy followed by 24 Gy/12 fractions of localised irradiation.

In our previous study [16], all patients ($n = 5$) with HCG-producing germinoma were alive without recurrence for a median follow-up period of 96 months. Conversely, the present results indicate a higher recurrence rate for HCG-producing germinoma ($n = 14$) than that of pure germinomas. Excluding 2 overlapping cases, we found 8 recurrent cases among a total of 17 patients. This has not previously been statistically clarified because of the rarity of HCG-producing CNS germinoma, although several reports have inferred it [3, 12, 15, 21]. Sano [15] reported a difference between 10 year survival rates, 91% for pure germinomas ($n = 43$) versus 80% for germinoma with syncytiotrophoblastic giant cells (STGC) ($n = 6$), which are equivalent to HCG-β producing cells. Yoshida and associates [21] treated 6 patients with germinoma containing HCG-producing cells with a combination of chemotherapy and irradiation, which resulted in a 100% recurrence rate and 50% mortality rate within 2 years. Balmaceda and colleagues [3] described 6 of 12 patients with recurrent germinoma showing elevated HCG-β. The elevated level of serum HCG-β is considered to be indicative of a higher risk of recurrence. The HCG-producing germinomas should be treated with a more intensive therapeutic protocol than pure germinomas [12].

GCTs, such as embryonal carcinoma, yolk sac tumour, or teratoma with malignant transformation, showed poor survival rates, as indicated in previous reports [9, 13, 15, 17–21, 32]. In selecting a therapeutic regimen, the CNS GCTs have been traditionally divided into two major groups, that is, germinomas and non-germinomatous GCTs, as an extrapolation from the gonadal GCTs [3, 8, 9, 11–14, 28–30, 32, 33]. For the CNS GCT, we have previously proposed the addition of another prognostic category of GCT between that of the pure germinoma and the highly aggressive GCTs [34]. These are HCG-producing germinoma and immature teratoma mixed with or without germinoma [8, 9, 15]. In addition, extensive, multifocal, or disseminated germinomas may be included in this group [16]. They should be distinguished from both highly aggressive GCTs and from pure germinomas and be regarded as an intermediate prognosis group.

Four life-threatening neoplasms were induced by radiotherapy. In our series, although small, the incidence of secondary neoplasm over 19 years was estimated to be 16.8% (95% confidence interval, 8.1–25.5%). The incidence of radiation-induced neoplasms may continue to increase with longer follow-up. Although published data are scarce on the incidence of late induction of CNS neoplasm by radiotherapy, this is supported by an estimated 20-year cumulative probability of a second cancer, reaching 12% in long-term survivors of cancer in childhood [35].

In conclusion, conventional radiation therapy, used alone, can be curative for germinomas, but at the same time it may be hazardous for young patients. In contrast, aggressive GCTs cannot be controlled by surgery and irradiation alone; a more intensive mode of therapy must be added. Between these two extremes, there is an intermediate prognostic category for which treatment may be plausibly planned with an intermediate intensity. A high risk of recurrence exists for HCG-producing germinomas and immature teratomas. While a single straightforward treatment for the whole disease spectrum is not appropriate, three risk-adapted stratagems

Table 4. *Classification of intracranial germ cell tumours for appropriate selection of management*

Good prognosis
Solitary pure germinoma
Mature teratoma
Intermediate prognosis
Germinoma with an elevated level of serum β-HCG
Extensive/multifocal/germinoma
Immature teratoma
Mixed germ cell tumours consisting of germinoma with either mature or immature teratoma
Poor prognosis
Teratoma with malignant transformation
Embryonal carcinoma
Yolk sac tumour
Choriocarcinoma
Mixed germ cell tumours including a component of embryonal carcinoma, yolk sac tumour, choriocarcinoma, or teratoma with malignant transformation

HCG, human chorionic gonadotropin.

(Table 4) [34] could be devised which would provide standard treatment for most patients and allow therapeutic studies to be conducted.

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