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Intracranial Germ Cell Tumour: Experience of a Singaporean Institution Over 11-Year Period

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ABSTRACT

Background: Intracranial germ cell tumours (IGCT) are rare. We present our experience in Therapeutic Radiology Department, National Cancer Centre, Singapore.

Methods: A retrospective study was conducted through case notes review on 25 patients with IGCT referred between January 1988 and January 1999.

Results: The median age at diagnosis was 13 years (range 6-22). The tumours were mainly pineal germinoma (72%). Median follow-up for living patients was 2.57 years (range 0.12-10.8). Median radiotherapy (RT) dose to whole brain, primary site and spine was 35.3, 54 and 30 Gys respectively. Four to six cycles of BEP or JEB chemotherapy (CM) were given in 10 patients. As for the whole study group, the seven-year overall survival (OS) and recurrence-free survival (RFS) were 86% (95% CI 72-100) and 78% (95% CI 60-100) respectively. The 10-year OS and RFS were 65% (95% CI 36-100) and 78% (95% CI 60-100) respectively. The germinoma group had 75% 10-year OS and 86% 10-year RFS. Mixed germinoma and non-germinoma germ cell tumours (NGGCT) group had 50% one-year RFS and 44% two-year OS. Acute side-effects of RT and CM were minimal. There was no statistically significant difference in side-effects when treatment modalities were compared.

Conclusion: In the treatment of intracranial germinoma, we recommend biopsy and CSRT. Primary chemotherapy (+/- low-dose cranial RT) should be used in the protocol or clinical trial settings. Chemo-radiotherapy is recommended for mixed germinoma and NGGCT. A multicentre trial is needed to address various controversial issues.

Keywords: Chemotherapy, Craniospinal radiotherapy, Germinoma, Intracranial germ cell tumour, Singaporean

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INTRODUCTION

Primary intracranial germ cell tumours (IGCT) are uncommon. They account for less than 2% of all intracranial malignancies before the age of twenty in the West, but contribute to 7.5% of all brain tumours in children in East Asia[1].

Although craniospinal radiotherapy (CSRT) has been the standard treatment for IGCT in the last few decades, there is still a lack of consensus on certain issues, e.g. role of chemotherapy, optimal radiotherapy dose and volume, etc. This is because firstly, the tumour is rare and secondly, patients with or without histology are all included in the data analysis of most studies[2].

With the founding of the Singapore Cancer Registry in 1967, there were 35 and 28 cases of IGCT registered for Singaporeans and non-Singaporeans respectively between 1968 and 1997 (unpublished data, Singapore Cancer Registry, 2000). The standard treatment for intracranial germinoma and non-germinomatous germ cell tumour (NGGCT) in Singapore had been CSRT and chemotherapy (with or without radiotherapy) respectively after biopsy or surgical resection. In recent years, there was a move towards using primary chemotherapy and lower-dose CSRT in intracranial germinoma so as to reduce the late effects of CSRT.

In view of this, the present study was undertaken to review the outcome and side-effects of treatments in patients with IGCT in the Singaporean setting.

PATIENTS AND METHODS

A list of 28 patients in total with IGCT, referred to the Therapeutic Radiology Department (TRD) of the Singapore General Hospital (SGH, now under National Cancer Centre) between January 1988 and January 1999, was generated from data-base computer. Retrospective study was carried out on 25 eligible patients only because the other three patients had no record of treatment in TRD. The medical records were reviewed after retrieving from TRD, Department of Neurosurgery in Tan Tock Seng Hospital (TTSH) and Department of Paediatric Medicine in KK Women's and Children's Hospital (KKH). The missing data was supplemented with telephone interviews and overseas correspondence.

The technique of CSRT for IGCT in this department was standard. In phase one, radiotherapy dose of 30 to 36 Gys in 1.6 to 1.8 Gys per fraction, five fractions a week, was given to the whole brain (enbloc with spinal cord at first to fourth cervical vertebral level), using lateral opposing fields. Median spinal dose of 30 Gys (range 19.8-36) in 1.1 to 1.8 Gys per fraction, five fractions a week, was given to equivalent depth of 90% isodose line from skin. The inferior border of the spinal field included the second or third sacral vertebra. The shifting junction technique was used to avoid hot spot between the cranial and spinal fields. Phase two cranial field was a boost to the primary site with margin, bringing the median total dose of 54.1 Gys (range 41.5-54.1) to the primary site. The boost was given using lateral opposing field, three-field technique or radiosurgery. Six MV photon beam was used. Complete blood picture was taken twice a week and only the spinal field was suspended when the platelet count was less than 100×10^9 per millilitre or white cell count fell below 3×10^9 per millilitre. There was small variation in cut-off point used among the consultants.

Cranial irradiation alone was given when combined with chemotherapy or when patient(s) had poor performance status. Shrinking field technique was used. Only six patients belonged to this category. Total median dose of 45 Gys (range 36-55.4) was given to the primary site.

Chemotherapy was given mainly in KK Women's and Children's Hospital by the paediatric medical oncologists. The protocol for the treatment of intracranial germinoma and NGGCT, was four to six courses of BEP or JEB chemotherapy (Bleomycin, Etoposide, CisPlatin/Carboplatin) with or without radiotherapy, after surgery or biopsy. BEP regimen was as follows: Bleomycin 15 mg/m^2 (Day 1), Etoposide 120 mg/m^2/day (Days 1-3), Cisplatin 100 mg/m^2 (Day 2), every 21 days. JEB regimen was as follows: Carboplatin 500 mg/m^2 (Day 1, 2), Etoposide 150 mg/m^2 (Days 1-3) and Bleomycin 15 mg/m^2 (Day 3), every 21 days. All were given by intravenous route. The glomerular filtration rate (GFR) was routinely checked with EDTA test prior to each cycle of chemotherapy. If GFR fell below 80 ml/1.73 m^2/min, Cisplatin would be changed to Carboplatin. The dose of Carboplatin was calculated according to the modified Calvert's formula as proposed by Newell et al[3].

Common Toxicity Criteria (CTC) was used in the assessment of treatment side-effects[4]. The acute side-effects analysed were nausea, vomiting, lethargy, bone marrow suppression (haemoglobin, total white cell, neutrophil and platelet count), episodes of neutropenic fever requiring admissions, sepsis and electrolyte disturbance. On the other hand, the subacute or late side-effects analysed were (a) neurological deficits including cranial, motor or sensory neuropathy; (b) visual problems including diplopia, blurred vision, parinaud syndrome, visual field defects, optic atrophy or blindness; (c) ambulatory difficulty including walking with aids, ataxia, paralysis, being wheelchair-bound or bed-bound; and (d) endocrine problems including amenorrhoea, precocious obesity and decrease in different pituitary hormones requiring replacement. Both intellectual dysfunction and skeletal growth were not analysed because of missing data.

The child psychologist was not routinely involved, unless there was a problem in learning, academic performance and coping with daily life. In such cases, formal assessment on the neuropsychological and intellectual function, e.g. Intelligence Quotient test (IQ), would be carried out. Visual field and endocrine functions (especially pituitary functions) were tested routinely prior to treatments and on follow-up if the initial results were abnormal.

STATISTICS

Kaplan-Meier methods were used to calculate the overall survival (OS) and recurrence-free survival (RFS) rates and the associated 95% Confidence Intervals (CI) for all 25 eligible patients in September 2000, using software S-PLUS[5]. In OS analysis, all living patients lost to follow-up were censored. The follow-up time was calculated from the date of primary diagnosis (by either biopsy or surgery) to the date of death, last follow-up or phone contact. As for RFS analysis, the follow-up time was calculated from the date of primary diagnosis to the date of relapse, death, last follow-up or phone contact. One patient who had recurrence before he was lost to follow-up, was regarded as "event" in the RFS analysis.

The post-treatment side-effects were compared between patients treated with chemotherapy alone and radiotheray alone (CSRT or whole brain RT). The significance of the difference was tested by Fisher's exact test.

RESULTS

Patient characteristics (Tables I and II)

There was a male predominance (7:1). The median age at diagnosis was 13 years (range 6-22). There were 18 Singaporean and seven non-Singaporean patients (Malaysia (4), Indonesia (2) and Brunei (1)). The majority (88%) were Chinese by race. Pure Germinoma consisted of 72% of the tumour. The sites of the tumour were mainly pineal gland (72%) and suprasellar region (16%). Two patients (8%) had tumour in both suprasellar and pineal regions.

Table I. Presentations (n= 25).

Variables	Tumour sites				
	Pineal (n = 18)	Suprasellar (n = 4)	Pineal and suprasellar (n = 2)	Basal ganglia (n = 1)	Total
Symptoms					
Visual problem	8	4	1		13
Headache	10	2			12
Vomiting	6				6
Drowsiness	2	3			5
Signs					
Hydrocephalus	18	1			19
Neurological deficit/ Ambulatory problem	8			1	9
Endocrine impairment	8	1			9

Two most common symptoms at presentation were visual problem (52%) and headache (48%). Pineal tumour was present in eight out of 13 patients (62%) with visual problems and 10 out of 12 patients (83%) with headache. On the other hand, three common presenting signs were hydrocephalus (requiring ventriculo-peritoneal shunts in 18 patients and third ventriculotomy in one patient), neurological deficit and endocrine impairment. Pineal tumour occurred in eight out of nine patients (89%) with ambulatory problem and eight out of nine patients (89%) with endocrine impairment.

All patients had histological diagnosis by either biopsy or resection (gross or partial), supplemented by radiological imaging (CT or MRI scans) prior to chemotherapy or radiotherapy. Serum markers were measured in 84% of the patients (21/25) but

Table II. Analysed cases (n=25)

Case	Age/ sex	Histology[1]	Primary sites[2]	Primary treatment[3]	Status[4]
1	18/m	G	b.gang	CSRT	NED, 3.7 years
2	10/m	G	P	CSRT	Dead, 7.7 years
3	22/m	G	P	CSRT	NED, 7.8 years
4	6/m	G	P	CM	NED, 2.4 years
5	10/m	G	P	CSRT	Lost to follow up, 0.2 years
6	7/m	G	P	CSRT	Lost to follow up, 1.5 years
7	13/m	G	P	CMRT	NED, 1.6 years
8	12/m	G	P	CSRT	NED, 7.5 years
9	7/m	G	P	CSRT	NED, 4.4 years
10	9/m	G	P	CMRT	NED, 6.2 years
11	16/m	G	P	CSRT	NED, 10.8
12	18/m	G	P	CSRT	NED, 7.9 years
13	13/f	G	SS	CMRT	NED, 1.9 years
14	16/m	G	SS	CM	Recurrence, 1.5 years, NED, 3.1 years
15	10/f	G	SS	CM	Recurrence, 2.5 years, NED, 4.4 years
16	19/m	G	SS,P	CMRT	NED, 2.6 years
17	14/m	G	SS,P	WBRT	NED, 2.4 years
18	17/m	G	P	CSRT	NED, 3.5 years
19	10/m	M	P	CMRT	NED, 2.2 years
20	19/m	M	P	CSRT	Dead, 0.3 years
21	19/m	M	P	CMRT	Recurrence, 1.1 years, NED, 2.6 years
22	10/f	M	SS	CMRT	Dead, 2.0 years
23	22/m	NG	P	CSRT	Recurrence, 0.9 years, Lost to follow up, 1.1 years
24	11/m	NG	P	WBRT	DOD, 0.6 years
25	12/m	NG	P	WBRT	Lost to follow up, 0.1 years

[1] G-Germinoma; M-mixed (Germinoma + NG); NG-non-germinoma.
[2] P-pineal; SS-suprasellar; b.gang-basal ganglia
[3] CSRT-craniospinal radiotherapy; WBRT-whole-brain RT; CMRT-chemo-RT; CM-chemotherapy
[4] NED-no disease; DOD-died of disease.

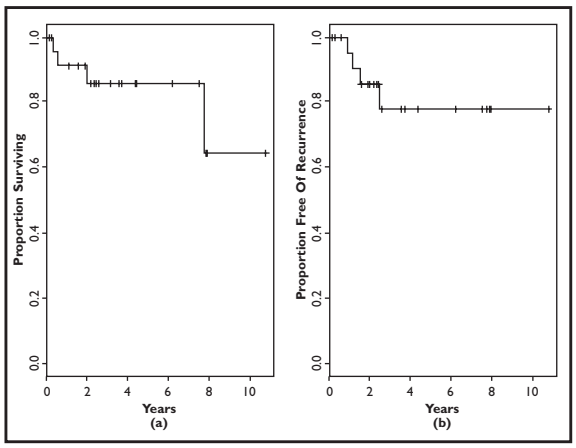

Fig. 1 Kaplan-Meier plot of (a) 10-year Overall survival and (b) 10-year Recurrence-free survival.

only 32% (8/25) had both serum and cerebrospinal fluid (CSF) markers measured. Spinal disease was assessed by either MRI scan of spine or CSF cytology in 10 patients and it was positive in one patient. This particular patient received CSRT and had remained free of disease with follow-up of 44 months.

Survival and Recurrence (Table II)

Twenty-one patients were alive with median follow-up of 2.57 years (range 0.12-10.8). There were four deaths. The seven-year OS and DFS for the whole study population were 86% (CI 72-100) and 78% (CI 60-100) respectively (Fig. 1). The 10-year OS (65% (CI 36-100)) was lower than 10-year DFS (78% (CI 60-100)) because of one death due to anaplastic glioma at follow-up time of 7.5 years. Eighteen patients with germinoma had 86% 10-year DFS and 75% 10-year OS. Seven others with mixed germinoma or NGGCT had 50% one-year DFS and 44% two-year overall survival. They fared worse than patients with germinoma.

Among the four deaths, the first patient had pineal germinoma in clinical remission after CSRT in July 1990, but died from anaplastic glioma of left cerebellum in March 1998 despite salvage chemotherapy. The patient initially received 43.2 Gys in 24 fractions to whole brain and then a boost to the primary site to a total dose of 54 Gys. We thought this was more likely to be second primary tumour because of the lower dose to cerebellum (45-54 Gys) as compared to radiotherapy-induced malignancy (>60 Gys).

The second patient had mixed germinoma and teratoma at pineal region and died from disease despite CSRT. In retrospect, chemotherapy could have been part of the treatment. The third patient with mixed germinoma and embryonal carcinoma at suprasellar region, died from sepsis after cranial radiotherapy followed by four courses of JEB chemotherapy. She had panhypopituitarism and high serum alpha-feto-protein (AFP) level on presentation. The fourth patient with pineal teratoma underwent surgical resection. He had cerebral herniation and suffered from global hypoxic cerebral injury. He received cranial radiotherapy of 36 Gys and eventually died of abdominal infection and Pseudomonas pneumonia.

In patients with germinoma, two out of three patients in chemotherapy-alone group recurred at a mean period of 23.8 months. They were all salvaged by CSRT. This gave a 100% 4-year overall survival. CSRT-group had 100% 5-year DFS at median follow-up time of 71 months. Chemo-radiotherapy group (n=4) had no recurrence at a median followup of 26.8 months.

Acute treatment side-effects

All patients tolerated *CSRT* or *WBRT* well with no acute toxicities, except for two patients who required a brief break because of CTC Grade 2 haematological toxicity (Haemoglobin 8.0 - <10.0 g/dl ; total leukocytes (2.0 - <3.0 x 10^9/litre).

Two patients receiving *chemotherapy* had temporary electrolyte disturbance (e.g. hyponatraemia due to Diabetis Insipidus) which was subsequently corrected. One patient developed neutropenic fever and recovered from Salmonella Group G infection. There was no death due to Sepsis. One patient had CTC grade 3 platelet toxicity (>10.0 - <50.0 x 10^9/L) and required transfusion.

The most serious acute surgical complication was the patient with pineal teratoma, who suffered from global hypoxic cerebral injury, spastic quadriplegia and coma after the surgical resection (see paragraph three in subsection on "survival and recurrence" above).

Subacute or late treatment side-effects

There was no statistically significant difference in post-treatment subacute or late side-effects between biopsy and surgery (unpublished data), as well as between chemotherapy and CSRT/WBRT (Table III). The lack of power to detect any difference may be due to the small number in both chemotherapy and CSRT/WBRT arms.

Intellectual dysfunction and impaired skeletal growth were not analysed because of inadequate data. Only two patients had formal Intelligent Quotient (IQ) assessment. Another patient receiving cisplatinum-containing chemotherapy, developed moderate high-frequency pure-tone hearing defect eight months after the beginning of first cycle of chemotherapy. He did not require any hearing aid and had regular follow-up by Ear, Nose and Throat specialist.

Table III. Post-treatment side-effects vs treatment modality (Fisher's Exact test; n=18) *

Post-treatment side-effects		Treatment CM** (n = 3)	Modalities CSRT/WBRT** (n = 15)	P value
Neurological	Yes	0	4	1
	No	3	11	
Visual	Yes	2	5	0.528
	No	1	10	
Ambulatory	Yes	0	4	1
	No	3	11	
Endocrine	Yes	2	2	0.108
	No	1	13	

* Seven patients treated with chemo-RT (CMRT) were not included in this analysis because this is chemo vs RT comparison.
** See footnotes (Table II)

DISCUSSION

With the advancement in stereotactic surgical technique, the risk of obtaining histological diagnosis of IGCT by biopsy alone is very small. However, surgical resection is not without risk. Matsutani and colleagues from the University of Tokyo Hospital and its affiliated hospitals, reported the largest single series of 153 patients on this tumour. It was their policy to treat all by surgical removal and histological verification, followed by radiation therapy with or without chemotherapy[6]. Surgery was done in 147 patients. All seven patients who died post-operatively, had marked intracranial hypertension with cerebral herniation prior to surgery. Nine patients had major complications, such as hemiparesis and mental retardation due to prolonged intracranial hypertension. Seven of them had pineal tumours. The overall mortality and morbidity rates were 4.8% and 6.1% respectively before 1980, and 2.6% and 2.6% respectively after 1980.

In our small series, 15 had surgery, in whom 10 were germinoma, two were mixed germinoma and three were NGGCT. Two patients had major complications of haemorrhage and pneumo-cranium respectively. The first patient had second resection for a recurrence 13.5 months after the initial surgery for pineal teratoma. Despite the complication, he made a reasonable recovery and received chemo-radiotherapy. He continued his rehabilitation and was alive at further follow-up time of 17 months. The second patient had global cerebral injury and his death had already been mentioned (see under "survival and recurrence" in the "Results section"). We would recommend biopsy alone for histological diagnosis, prior to radiotherapy or chemotherapy as there is inherent risk with surgery.

With radiotherapy alone, the survival of IGCT is sharply divided between germinoma and NGGCT. Dearnaley and colleagues from Royal Marsden Hospital, reported 80% to 100% survival for germinoma, but only 20% to 50% for NGGCT[7]. Hence, the combination of chemotherapy and radiatherapy is appropriate for the latter[8].

There is, however, more controversy in the treatment of intracranial germinoma. The conventional treatment for this tumour is CSRT, yielding 65% to 95% five-year survival[9]. Yet the toxicity is the concern. This concern is legitimate as the quality of life becomes a real issue in long-term survivors of curable tumour. To address this concern, there are studies undertaken with smaller treatment volume, lower radiotherapy dose and the use of primary chemotherapy without radiotherapy. The possible cost though is the decreased survival.

Sutton and colleagues conducted a study to assess the quality of life (QOL) of 27 patients treated for intracranial germinoma with biopsy followed by standard prophylactic whole-neuraxis radiation therapy between 1976 and 1996[10]. The doses given were 36 Gys to the neuraxis, 50.4 Gys to the primary site and 45 Gys to nodular spinal metastatic lesions. The mean follow-up was 9.8 years. The mean age at diagnosis was 16.9 years (range 11-42). The short-form-36 and Functional Assessment of Cancer therapy QOL questionnaires were used, supplemented by data regarding height and weight, medications, ability to work and educational achievement. Compared with normal population of 474 individuals, these patients scored equal to or higher in the areas of physical, bodily pain, vitality, social function, emotional and mental health, except physical functioning (mean, 71 versus 92 for the control group, $p<0.00005$) and general health (mean 58 versus 77 for control group, $p<0.00005$). Age at radiation did not correlate with QOL. The authors concluded that the QOL after whole-neuraxis irradiation for marker-negative germinoma was generally good.

Aoyama and associates reported on 41 patients with biopsy-proven germinomas[11]. The 10-year relapse-free survival was 90%, 76% and 22% for those treated with craniospinal, whole-brain and local radiation respectively. Local fields without ventricular irradiation for localised germinoma could not be recommended. On the other hand, the literature review done by Lindstadt et al[12] and the experience of Joint Center for Radiation Therapy[2] showed that no biopsy-proven germinoma patient treated with CSRT had ever failed in the spine.

There were conflicting results of different studies employing different radiation doses to the primary site. The doses ranged from 40 to 55 Gys[13]. In Kyoto University series, the 10-year relapse-free survival was 88% and there was no significant difference in relapse-free survival or overall survival among patients with histological confirmation receiving doses in the range from 43.2 to 62 Gys[14]. Other

investigators concluded that there was increased relapse rate if less than 40 Gys were given[15]. Conclusions were difficult to draw because of the variation in patient selection, radiation dose and definition of local radiation volume. Both germinoma and NGGCT patients were analysed together in these series[16]. However, in general, most series reported a high rate of primary tumour control after greater than 40 Gys were given to the local tumour.

In an attempt to reduce radiation dose and volume, some studies employed the use of chemotherapy. Bouffet and colleagues reported on the experience of French Society of Paediatric Oncology in treating 51 patients with localised germinoma with 47 having histological diagnosis[17]. This was a multicentre single-arm study. Fifty patients received four courses of chemotherapy (alternating etoposide-carboplatin and etoposide-Ifosfamide) with 40 Gys local irradiation and one patient was given CSRT because of intolerance to chemotherapy. With median follow-up of 42 months, there were four relapses, three of whom were salvaged with chemotherapy alone or chemo-radiotherapy. The three-year survival is 98% (CI 86.6-99.7) and three-year event-free survival is 96.4% (CI 86.2-99.1). In another study reported by Sawamura and colleagues[18], 17 patients with germinomas, received chemotherapy with a variety of different drugs followed by 24 Gys of local radiation therapy. The authors reported 100% survival and 94% two-year progression-free survival. Although the results from these two studies were very good and promising, they were still early results. More mature data is awaited before we have definite answers on optimal radiation dose and volume for localised germinoma.

Primary chemotherapy alone was used as a novel approach to treat intracranial germinoma in the First International Central Nervous System Germ Cell Tumour Study[19]. The median follow-up was 31 months. Four cycles of carboplatin, etoposide and bleomycin were given. Complete responders received two further cycles whereas others received two cycles intensified by cyclophosphamide. The complete response rate for germinoma was 84%. The 45 patients with germinoma relapsed in 50% with 84% two-year survival. The authors concluded that although the result of primary chemotherapy was encouraging, it should continue to be used only in the setting of formal clinical trials.

In our series, three patients who received primary chemotherapy had a median follow-up of 2.46 years only. Longer follow-up is needed. There is little late toxicity after treatment with CSRT at a median follow-up of 5.92 years. There is some difficulty in following up the seven non-Singaporean patients once they return to their home countries after treatment.

The documentation of late effect in our centre can be improved, especially in the area of neuropsychological and intellectual functions, which are better assessed by a child psychologist. It is recommended that the child psychologist should be routinely involved. Therefore, more child psychologists are needed in local settings. In addition, it is hoped that with the commencement of Late Effect Clinics in Singapore, more coordinated attention can be put into the follow-up of treatment-related late effects.

CONCLUSION

This retrospective study has provided another perspective in Asian setting, although it is a small series. It is certainly essential to have more collaboration among different cancer centres (local and international) for multicentre prospective trials, addressing various controversial questions on the optimal management of IGCT in time to come. Until then, we recommend CSRT and combination chemo-radiotherapy to be the standard treatment for intracranial germinoma and NGGCT respectively. Primary chemotherapy with or without lower-dose cranial radiotherapy in the treatment of intracranial germinoma should be given in the context of protocol or clinical trial settings.

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