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CLINICAL STUDY

Pure germinomas of the central nervous system: treatment strategies and outcomes

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Abstract To evaluate the role of chemotherapy and radiation therapy in the treatment of pure germinomas of the central nervous system (CNS). We reviewed a historical cohort of 79 patients between the ages of 3–35 years who received definitive treatment for newly diagnosed, pure CNS germinoma between 1985 and 2010 at the University of California, San Francisco (UCSF). Median age at diagnosis was 15 years (interquartile range, IQR 12–20 years) and 61 (77.2 %) patients were male. Median follow-up for the cohort was 111.1 months (IQR 45.7–185.1 months). Five-year PFS rate was 86.4 % (95 % CI 76.1–92.4) and 5 year OS rate was 93.0 % (95 % CI 84.1–97.1). Median PFS was 104.6 months (IQR 41.4–170.1 months). Fourteen patients progressed and 8 died of their disease. Patients who received focal irradiation (XRT) and chemotherapy had a significantly higher rate of progression compared to those who received whole brain irradiation (WBI) or whole ventricle irradiation (WVI). Three of 8 patients had a PR to chemotherapy and received focal XRT progressed whereas only 1 of 9 patients who had a CR to chemotherapy who went on to receive focal XRT progressed. Elevation of hCGβ > 50 mIU/ml was not significantly associated with disease progression (HR 5.64, 95 % CI 0.97–32.7, $p = 0.054$). Patients treated with WBI or WVI with or without chemotherapy achieve better disease control compared to patients treated with focal XRT + chemotherapy.

Keywords Pure germinoma · Radiation therapy · Chemotherapy · bHCG

Introduction

Germ cell tumors of the central nervous system (CNS) represent 3–5 % of all brain tumors in children. Pure germinomas account for two-thirds of all germ cell tumors and are most often located in the pineal and/or pituitary region of the brain [1, 2]. Optimal management for intracranial germinomas is controversial [3–6]. Historically, the standard management for all germinoma patients included craniospinal irradiation (CSI) (25–35 Gy) with a boost to the tumor bed (10–25 Gy). This treatment approach

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achieves high cure and overall survival rates, but has been called into question due to significant morbidity [7–10].

Reductions of the radiation field size and dose have been proposed as a way to limit long-term radiation toxicity because of the low incidence of spinal relapse associated with intracranial disease [7], [10–12] whole brain irradiation (WBI) or whole ventricle irradiation (WVI) followed by a boost to the tumor bed has been shown to achieve excellent local control [8, 9, 13]. The integration of chemotherapy into treatment regimens has been tried to allow for further reductions in XRT dose [6, 10]. However, limiting radiation therapy to the tumor bed alone may lead to a high rate of intracranial relapse, even with the addition of chemotherapy [8, 10, 11, 13].

It remains unclear if hCGβ levels can be used as a prognostic marker to help guide treatment decisions. Although patients with elevated hCGβ levels may have poorer survival [14], many studies have found no difference in clinical outcome among patients with elevated hCGβ levels versus those with normal tumor marker levels for pure germinomas [11, 15, 16]. In the current ongoing Children's Oncology Group Study, patients with hCGβ level up to 100 IU/ml will be treated per the pure germinoma strata if AFP levels are within normal levels.

The current study evaluates a historical cohort of patients treated at the University of California, San Francisco (UCSF) from 1985 to 2010 with the intention of comparing the efficacy three treatment groups: focal XRT and chemotherapy, WVI/WBI and chemotherapy, and WVI/WBI alone in the management of pure intracranial germinomas. Further, the study examines the prognostic significance of elevated hCGβ levels.

Methods and materials

The UCSF Cancer Registry was searched using keywords designed to retrieve all patients with pure intracranial germinomas treated at UCSF between 1985 and 2010. Patients were excluded if: (1) primary tumor site was outside the CNS (2) treatment was not performed at UCSF; (3) initial treatment was unknown; (4) no confirmatory pathology was available; and/or (5) patients were lost to follow-up within 2 weeks after initial treatment. There were no cases for which tumor markers were elevated, but biopsy specimens were unavailable. The following data were collected from the medical record: demographic information, details regarding treatment such as radiation and chemotherapy, serum and CNS tumor markers, and clinical outcome. The extent of disease was determined by reviewing the pre-operative imaging reports (MRI/CT scan) and post-operative notes. Patients were classified based on imaging (MRI/CT scan) as having a solitary lesion (pineal or pituitary), bifocal lesions (pineal and pituitary), multifocal lesions (multiple intracranial lesions), other intracranial lesion (solitary lesion outside pineal or pituitary gland) or disseminated disease (spinal cord involvement). Staging practices varied depending upon the provider and time period of diagnosis. In 56 cases, details of AFP levels (51 CSF) were available and all were within normal range.

We determined the specific treatment used by reviewing chemotherapy and radiation therapy records, as well as operative reports. A radiation field restricted to the tumor volume was defined as focal XRT, a field that extended to include the whole ventricular volume was defined as WVI, a field that included the whole brain was defined as WBI, and a field that included the brain and spine was defined as CSI. The pathology for all cases was determined or reviewed by a neuropathologist (AWB or TT) at UCSF.

Patients without documented progression were assumed to be progression-free at the last day of documented contact. Patients were followed by clinical examination as well as with imaging studies and tumor marker assays. Clinical examination and imaging studies (MRI and/or CT) were recommended every 3–4 months during the first 2 years following the completion of therapy and every 6 months thereafter unless additional examinations were clinically warranted. In order to confirm relapse, brain and spine MRI and tumor markers assays were used and biopsies were performed in some cases.

PFS was defined as time between initial diagnosis and first evidence of progression and/or recurrence or death whichever came first. We defined progression/recurrence either based on imaging, increase in hCGβ or based on clinical documentation of disease recurrence and/or progression. If the patient was alive with no documented recurrence, the patient was censored for PFS at date of last follow-up. Overall survival (OS) was defined as the time between initial diagnosis and death from any cause. Patients alive were censored at last follow-up.

Curves for PFS and OS were generated using the Kaplan–Meier method and were compared with the log-rank χ^2 test. A Cox proportional hazards regression model was used to assess the association between primary treatment and outcome adjusting for other factors including age, gender, decade of diagnosis, and hCGβ elevation. Two-tailed Pearson's Chi square and Fisher exact tests evaluated the relationship between tumor location, primary treatment, hCGβ elevation, decade of diagnosis, age and gender. STATA version 12.1 was used for all statistical analyses. This study was approved by the Committee for Human Research, the institutional review board at UCSF.

Results

Patient characteristics

Patient characteristics and treatment details are described in Table 1. Median age at diagnosis was 15 years (IQR 12–20 years), with 53 (67.1 %) patients age 18 or under at diagnosis. Sixty-one (77.2 %) patients were male. The median follow-up for all patients was 111.1 months (interquartile range 45.7–185.1 months) and 115.5 months (IQR 56.1–192.4 months) for the 65 patients without progression. Fifty-five patients were diagnosed with a solitary lesion, 11 patients were diagnosed with bifocal lesions, 4 were diagnosed with multifocal, intracranial disease, and 3 patients were diagnosed with disseminated disease. Three of the 55 patients with solitary lesions had tumor sites outside of the pineal gland or pituitary region (right thalamic, right frontal lobe, cervicomedullary junction). For 6 patients, the data on lesion location was not available.

Treatment characteristics

Table 2 summarizes treatment used separated by extent of disease. For 16 patients, the details of radiation treatment could not be recovered. The mean dose of radiation delivered in the remaining patients (n = 57) was 45.2 Gy (IQR 40–50.4 Gy). The dose delivered did not differ significantly among patients who received focal XRT and chemotherapy, WBI or WVI alone, or WBI or WVI and chemotherapy (ANOVA, $p = 0.4$). There was a treatment shift over time from 1985 to 2010 with an increase in the number of patients who received focal XRT and chemotherapy compared to other treatments between 1990s and 2000s (Table 3 Pearson's Chi square, $p = 0.003$), and a significant decrease in the number of patients who received WBI or WVI alone compared to other treatments from the 1990s to 2000s (Pearson's Chi square, $p = 0.01$). Patients with solitary and bifocal lesions received CSI at significantly lower rates than patients with other lesions (Pearson's Chi square, $p < 0.001$). We did not identify any treatment differences based on age or gender.

For patients (n = 45) with intracranial lesions who received chemotherapy, details of their regimens were available for 33 patients. Chemotherapy regimen varied as a modification of standard of care, but the majority (n = 21) of patients received 4–6 cycles (21 day cycles) of carboplatin (300 mg/m^2/dose × 2 days or 600 mg/m^2/dose × 1 day) and etoposide (150 mg/m^2/dose × 3 days). Twelve patients received 3–6 (21 day cycles) of other regimens for which the entirety of details on dose and timing is not available. These regimens included 3 patients who received alternating cycles of carboplatin (300 mg/m^2/dose × 2 days or 600 mg/m^2/dose × 1 day) and etoposide (150 mg/m^2/dose × 3 days) and etoposide (100 mg/m^2/dose × 5 days) and ifosfamide (1800 mg/m^2/dose × 5 days) and 3 patients who receive 4–6 cycles of carboplatin, etoposide, and bleomycin (dosages unknown). Six patients received 3–6 cycles of other regimens.

Twenty-five patients received neo-adjuvant chemotherapy with documentation of response to therapy. Fourteen patients had a partial response (PR) to chemotherapy and 11 patients had a complete response (CR). The remaining patients' responses to chemotherapy were not documented because they had a gross total resection (n = 2) or received chemotherapy after radiation (n = 6). Eight patients had a PR to chemotherapy and went on to receive focal XRT and 9 patients had a CR to chemotherapy and went on to receive focal XRT. Six patients had a PR to chemotherapy

Table 1 Patient characteristics and treatment details

	Number of patients
Age at diagnosis	
≤11 years	16
12 to ≤18 years	40
>18 years	23
Sex	
Male:Female	61:18
Decade of diagnosis	
1985–1989	14
1990–1999	33
2000–2010	32
Tumor site	
Solitary (Pineal or Pituitary)	52 (34:18)
Solitary other[a]	3
Bifocal	11
Multifocal	4
Disseminated	3
Unknown	6
Treatment	
Focal radiation	1
Focal radiation + chemotherapy	20
WBI	8
WBI + chemotherapy	6
WVI	8
WVI + chemotherapy	10
CSI	10
hCGβ mIU/ml (serum and CSF): <5	41
5 to ≤50	16
51 to ≤100	4
>100	2

WBI whole brain irradiation, *WVI* whole ventricular irradiation, *CSI* craniospinal irradiation

[a] 1 right thalamic, 1 right frontal lobe, 1 cervicomedullary junction

Table 2 Treatment details according to disease status

Treatment	Site			
	Solitary	Bifocal	Multifocal	Disseminated
Focal radiation	1	–	–	–
Focal radiation + chemotherapy	16	4	–	–
WBI	8	–	–	–
WBI + chemotherapy	3	1	2	–
WVI	7	1	–	–
WVI + chemotherapy	7	2	1	–
CSI	1	–	1	–
CSI + chemotherapy	2	2	1	3

CSI craniospinal irradiation, *WBI* whole brain irradiation, *WVI* whole ventricular field irradiation

Table 3 Treatment details according to decade

Treatment	Decade		
	1980s	1990s	2000s
Focal radiation	0	1	0
Focal radiation + chemotherapy	0	5	15
WBI	4	3	1
WBI + chemotherapy	0	4	2
WVI	1	6	1
WVI + chemotherapy	1	4	5
CSI	1	1	0
CSI + chemotherapy	0	4	4

CSI craniospinal irradiation, *WBI* whole brain irradiation, *WVI* whole ventricular field irradiation

and received WVI/WBI, whereas only one patient who had a CR received WVI/WBI.

Treatment outcomes

Median PFS for the entire cohort was 104.6 months (IQR 41.4–170.1 months). Fourteen patients progressed and 8 died of their disease. Overall PFS and OS rates at 5 years were 86.4 % (95 % CI 76.1–92.4) and 93.0 % (95 % CI 84.1–97.1), respectively (see Fig. 1).

Patterns of relapse

Of the 14 patients who relapsed, 8 had solitary lesions of the pineal or pituitary gland, 1 had solitary disease of the cervicomedullary junction, 3 had bifocal lesions, 1 had multifocal, and 1 had disseminated disease (Table 4). Four out of six patients who received focal radiation and relapsed did so outside of the radiation field. None of the patients with focal lesions had a documented relapse within the spinal cord regardless of the radiation field used. However, one patient who had a bifocal lesion who received WVI had a spinal cord relapse and one patient who had multifocal disease who received WBI had a spinal relapse.

Three of 8 patients who had a PR to chemotherapy and received focal XRT progressed whereas only 1 of 9 patients who had a CR to chemotherapy who went on to receive focal XRT progressed. No patients who had a PR to chemotherapy and had WVI/WBI progressed (n = 6). One patient who had a CR to chemotherapy and received WVI/WBI progressed (n = 1).

Outcomes by treatment for solitary and bifocal lesions

Univariate analysis is shown in Table 5. Patients treated with focal radiation therapy had shorter PFS compared to patients treated with WBI or WVI (with or without chemo) (HR 5.4, 95 % CI 1.22–24.3, $p = 0.026$). PFS curve by treatment is shown in Fig. 1. The PFS at 10 years for patients who received focal XRT + chemotherapy, WBI or WVI + chemotherapy, and WBI or WVI alone were 77.2 % (95 % CI 48.9–91.1), 85.1 % (95 % CI 52.3–96.1), and 92.3 % (95 % CI 56.6–98.8), respectively.

Prognostic significance of hCGβ for solitary and bifocal lesions

hCGβ (48:8 CSF:serum) levels were elevated in 13 of 56 patients between 5–50 mIU/ml in the serum and/or CSF, in 4 of 57 patients between 51 and 100 mIU/ml in the serum and/or CSF, and in 1 of 57 patients greater than 100 mIU/ml (485 mIU/ml). Elevation of hCGβ >50 mIU/ml was not significantly associated with disease progression (HR 5.64, 95 % CI 0.97–32.7, $p = 0.054$).

Discussion

In this report, we describe the treatment of pure CNS germinomas at one institution between 1985 and 2010. The disease control rates for solitary or bifocal lesions in

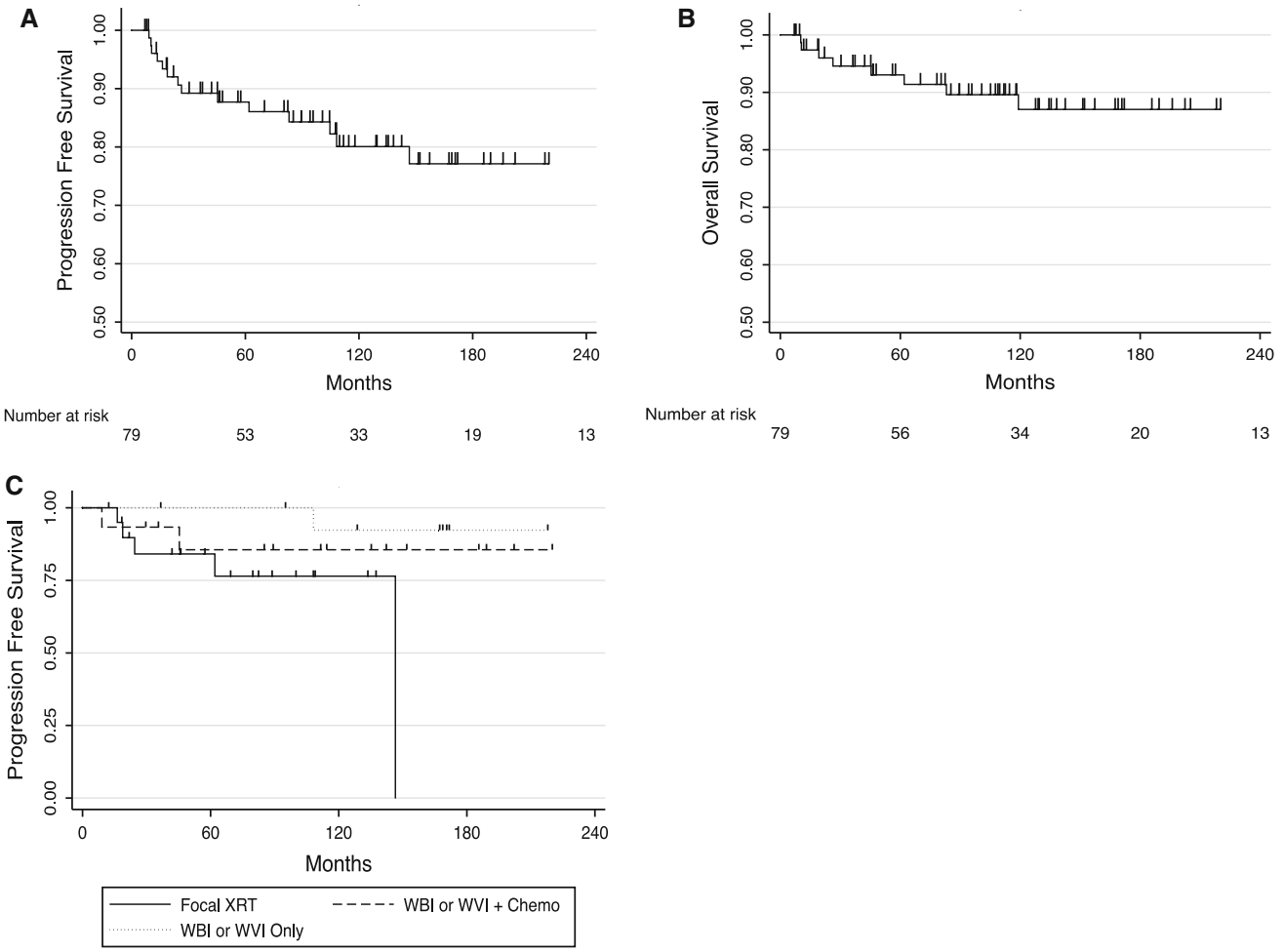

Fig. 1 **a** Progression-free survival and **b** overall survival for all patients (N = 123). **c** Progression-free survival according to treatment group for solitary or bifocal lesions. Focal radiation + chemotherapy (Focal XRT): *solid line*. Whole ventricle irradiation + chemotherapy (WBI or WVI): *dashed line*. Whole ventricle irradiation alone (WBI or WVI): *dotted line*

patients undergoing WBI or WVI with chemotherapy and without chemotherapy, were significantly better than focal XRT and chemotherapy. Among those patients who receive focal XRT + chemotherapy, those who initially have a complete response to chemotherapy appear to have better survival rates.

The appropriate radiation field size and dosage for pure CNS germinoma treatment remains a matter of debate. Previously reported small phase II series of patients found good control rates for focal XRT with 1.5–2 cm margins [3, 17, 18] that was confirmed in larger studies [19, 20]. However, when both dose and field size were reduced, focal XRT was associated with high progression rates in the ventricular system outside of the radiation field [6, 10]. Our data support these findings with increased intracranial recurrence rates among patients who received focal XRT.

However, unlike prior studies, our study suggests that there may be a role for focal XRT among patients who have a complete initial response to chemotherapy. In our study, among patients who had a complete response to chemotherapy and went on to receive focal XRT, only 1 of 9 patients progressed whereas 3 of 8 patients who had a partial response progressed. This contrasts the SIOP CNS GCT 96 study, which found that 5 of 7 patients who relapsed after focal XRT had a complete response to chemotherapy [6].

Maximum levels of hCGβ in pure germinomas as well as its prognostic significance remain topics of debate. Recent studies have shown no prognostic significance of hCGβ levels [10, 11, 15] although prior studies have found a significant survival advantage in non hCGβ-secreting germinomas [14]. The Japanese germ cell tumor group currently treats localized germinomas irrespective of hCGβ on the same treatment protocol [21]. Our study showed failed to show a significant association between elevated hCGβ levels above 50 mIU/ml and higher rates of progression in patients who have solitary or bifocal lesions. However, our data are limited in that only 5 patients had

Table 4 Patients characteristics, site, and type of relapse with regard to radiation field

Patient number	Primary disease site	Radiation treatment	Time to relapse (months)	Site of relapse
1	PINEAL GLAND	Focal	18.8	R frontal horn
2	PINEAL GLAND	Focal	24.4	L frontal lobe
3	PINEAL GLAND	Focal	62	Cervicomedullary junction
4	PITUITARY GLAND	Focal	104.6	Suprasellar/Pineal/Ependymal
5	PITUITARY GLAND	Focal	146.6	Leptomeningeal/L frontal lobe
6	PINEAL GLAND	WBI	108.2	Lateral/Third ventricle
7	BIFOCAL	Focal	16.3	Anterior and posterior horns/ Hypothalamic
8	BIFOCAL	WBI	45.4	Suprasellar/Pineal
9	BIFOCAL	WVI	9.1	T11 to L5-S1
10	MULTIFOCAL	WBI	13.5	Subependymal spread/Frontal horns/Pineal/Spine
11	DISSEMINATED	CSI	10.2	Pineal
12	CERVICOMEDULLARY JUNCTION	CSI	83.1	R cerebellar/L vermis/Spine
13	PINEAL GLAND	Unknown	10.5	Unknown
14	PINEAL GLAND	Unknown	26.3	Pineal

CSI craniospinal irradiation, *WBI* whole brain irradiation, *WVI* whole ventricular field irradiation

Table 5 Univariate analysis of PFS in patients with solitary and bifocal intracranial lesions

Characteristic	Hazards ratio	95 % CI	*p* Value
Radiation field: Focal vs WBI or WVI	5.4	1.22–24.3	0.026
Elevation of hCGβ > 50 mIU/ml	5.6	0.97–32.7	0.054
Age at diagnosis (years)	0.98	0.89–1.07	0.63
Male gender	1.93	0.42–8.82	0.397
Decade of diagnosis (ref. 1980s)			
1990s	2.7	0.32–22.2	0.36
2000s	4.1	0.44–36.7	0.21

elevation of hCGβ > 50. Of these, 3 received focal XRT and chemotherapy, and 2 received WVI and chemotherapy. Therefore, further research may be necessary to determine if more aggressive treatment may be warranted when considering patients with elevated hCGβ levels.

We found that 4 out of 14 patients relapsed between 5 and 10 years after initial treatment and one patient relapsed after 10 years, confirmed by pathology and/or markers. It is possible that these relapses actually represent second malignancies; however, late relapse in pure germinoma patients is not uncommon [10, 22, 23]. Therefore it is important that these patients are followed long-term and to improve our understanding of the relapse patterns in these patients.

Our study evaluates a large cohort of patients treated at a single institution with a relatively long follow-up of approximately 10 years. In our study, all patients had pathological confirmation by a UCSF neuro-pathologist, and regular follow-up was documented. However, the inherent constraints of a retrospective study with a relatively small sample size limit the conclusions we can draw from our findings with variability in treatment and follow-up. Treatments were not allocated randomly and selection bias may have occurred. Further, imaging, radiotherapy, and treatment techniques have changed overtime, which also may bias our findings. Specifically, MRI was not widely available until the early 1990s. During this time, treatment gradually progressed from larger radiation fields to smaller fields with the addition of chemotherapy. Further, the sample (and sub-sample) size for patients led to analysis with point estimates of hazards ratios with wide confidence intervals. Analysis of patients with different extents of disease was too small to compare PFS and OS for these patients by treatment or any other independent variable. It is also possible that recurrences were related to inadequate RT field size.

We highlight the shortcomings of focal XRT + chemotherapy as primary treatment for intracranial germinoma. Among patients with solitary or bifocal lesions, those who received focal XRT + chemotherapy were at significantly increased risk of progression compared to patients who received WVI or WBI. However, our study suggests that there may be a role for focal XRT among patients who have a complete initial response to chemotherapy, but final conclusions cannot be drawn due to limited sample size. Further studies with longer follow-up and a larger cohort of patients are necessary to assess the role of combined therapy and the prognostic significance of hCGβ levels in the treatment of germinomas.

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Conflict of interest None.

References

1. Packer RJ, Cohen BH, Cooney K (2000) Intracranial germ cell tumors. Oncologist 5(4):312–320
2. Echevarria ME, Fangusaro J, Goldman S (2008) Pediatric central nervous system germ cell tumors: a review. Oncologist 13(6):690–699
3. Aoyama H, Shirato H, Ikeda J, Fujieda K, Miyasaka K, Sawamura Y (2002) Induction chemotherapy followed by low-dose involved-field radiotherapy for intracranial germ cell tumors. J Clin Oncol 20(3):857–865
4. Fujimaki T (2009) Central nervous system germ cell tumors: classification, clinical features, and treatment with a historical overview. J Child Neurol 24(11):1439–1445
5. Matsutani M (2009) Pineal germ cell tumors. Prog Neurol Surg 23:76–85
6. Calaminus G, Kortmann R, Worch J et al (2013) SIOP CNS GCT 96: final report of outcome of a prospective, multinational nonrandomized trial for children and adults with intracranial germinoma, comparing craniospinal irradiation alone with chemotherapy followed by focal primary site irradiation for patients with localized disease. Neuro-oncology 15(6):788–796
7. Haas-Kogan DA, Missett BT, Wara WM et al (2003) Radiation therapy for intracranial germ cell tumors. Int J Radiat Oncol Biol Phys 56(2):511–518
8. Rogers SJ, Mosleh-Shirazi MA, Saran FH (2005) Radiotherapy of localised intracranial germinoma: time to sever historical ties? Lancet Oncol 6(7):509–519
9. Shikama N, Ogawa K, Tanaka S et al (2005) Lack of benefit of spinal irradiation in the primary treatment of intracranial germinoma: a multiinstitutional, retrospective review of 180 patients. Cancer 104(1):126–134
10. Alapetite C, Brisse H, Patte C et al (2010) Pattern of relapse and outcome of non-metastatic germinoma patients treated with chemotherapy and limited field radiation: the SFOP experience. Neuro-oncology 12(12):1318–1325
11. Ogawa K, Shikama N, Toita T et al (2004) Long-term results of radiotherapy for intracranial germinoma: a multi-institutional retrospective review of 126 patients. Int J Radiat Oncol Biol Phys 58(3):705–713
12. Lafay-Cousin L, Millar BA, Mabbott D et al (2006) Limited-field radiation for bifocal germinoma. Int J Radiat Oncol Biol Phys 65(2):486–492
13. Jensen AW, Laack NN, Buckner JC, Schomberg PJ, Wetmore CJ, Brown PD (2010) Long-term follow-up of dose-adapted and reduced-field radiotherapy with or without chemotherapy for central nervous system germinoma. Int J Radiat Oncol Biol Phys 77(5):1449–1456
14. Sawamura Y, Ikeda J, Shirato H, Tada M, Abe H (1998) Germ cell tumours of the central nervous system: treatment consideration based on 111 cases and their long-term clinical outcomes. Eur J Cancer 34(1):104–110
15. Ogino H, Shibamoto Y, Takanaka T et al (2005) CNS germinoma with elevated serum human chorionic gonadotropin level: clinical characteristics and treatment outcome. Int J Radiat Oncol Biol Phys 62(3):803–808
16. Finlay J, da Silva NS, Lavey R et al (2008) The management of patients with primary central nervous system (CNS) germinoma: current controversies requiring resolution. Pediatr Blood Cancer 51(2):313–316
17. Buckner JC, Peethambaram PP, Smithson WA et al (1999) Phase II trial of primary chemotherapy followed by reduced-dose radiation for CNS germ cell tumors. J Clin Oncol 17(3):933–940
18. Kretschmar C, Kleinberg L, Greenberg M, Burger P, Holmes E, Wharam M (2007) Pre-radiation chemotherapy with response-based radiation therapy in children with central nervous system germ cell tumors: a report from the children's oncology group. Pediatr Blood Cancer 48(3):285–291
19. Bouffet E, Baranzelli MC, Patte C et al (1999) Combined treatment modality for intracranial germinomas: results of a multicentre SFOP experience. Société Française d'Oncologie Pédiatrique. Br J Cancer 79(7–8):1199–1204
20. Matsutani M (2001) Combined chemotherapy and radiation therapy for CNS germ cell tumors–the Japanese experience. J Neurooncol 54(3):311–316
21. Matsutani M. Treatment of intracranial germ cell tumors: The second phase II study of Japanese GCT study group. *Neuro-oncology.* 2008;420
22. Kamoshima Y, Sawamura Y, Ikeda J, Shirato H, Aoyama H (2008) Late recurrence and salvage therapy of CNS germinomas. J Neurooncol 90(2):205–211
23. Von Rohr E, Gonner F, Schroth G, Cerny T (1999) Relapse and subarachnoid dissemination of a pineal germinoma 14 years after radiation therapy. J Clin Neurosci 6(3):247–249