Predictors of long-term survival following postoperative radiochemotherapy for pathologically confirmed suprasellar germ cell tumors

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Abstract. The aim of this study was to evaluate the predictors of long-term survival following postoperative therapy for suprasellar germ cell tumors (GCTs). A total of 23 patients with pathologically confirmed suprasellar GCTs were reviewed between April, 1987 and October, 2008. The predictors were identified with a univariate Cox proportional hazards model and the results were used to group patients according to outcome. The overall survival (OS) and progression-free survival (PFS) rates for the good- and poor-prognosis two groups were estimated with Kaplan-Meier analysis, with log-rank tests used to assess differences between the groups. The OS rate for all patients was 82.6% at 5 and 72.9% at 10 years. Lesion size (2-4 vs. >4 cm) and pathological type (pure germinoma vs. mixed GCT) were the only significant predictors of OS ($P<0.05$). The OS rate for the good-prognosis group was 92.9% at both 5 and 10 years, whereas the corresponding rates for the poor-prognosis group were 66.7 and 40.0%, respectively ($P=0.020$). The PFS rate for the good-prognosis group was 92.9% at 5 and 85.7% at 10 years, whereas the corresponding PFS rates for the poor-prognosis group were 44.4 and 33.3%, respectively ($P=0.007$). Lesion size and histology predicted outcome following postoperative therapy for suprasellar GCT. Therefore, pathological diagnosis is recommended whenever possible, as histology may dictate the choice of treatment.

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Introduction

Primary germ cell tumors (GCTs) of the central nervous system (CNS) in children are common in Asia, where they account for 15-18% of all CNS tumors of childhood, compared to 3-5% in the United States and Europe. The peak incidence for CNS GCTs is at 10-12 years of age, although it varies by tumor histology and differentiation, with non-germinomatous GCTs (NGGCTs) being more common in younger children and pure germinomas being more common among older patients. The majority of the CNS GCTs arise from primordial germ cells in structures surrounding the third ventricle. The majority of these tumors (94%) develop along the midline, most often from the pineal gland (which produces primarily NGGCTs), followed by tumors arising in the suprasellar cisterns (which are most often germinomas) (1-3). NGGCTs and mixed GCTs often consist of one or more histopathological subtypes, such as mature teratoma, immature teratoma, teratoma with malignant transformation, embryonal carcinoma, yolk sac tumor and choriocarcinoma. Cranial NGGCTs are generally associated with worse outcomes compared to cranial germinomas (4). Surgery followed by radiochemotherapy has achieved excellent survival rates for patients with intracranial germinomas (5-10). Suprasellar germinomas commonly present as diabetes insipidus, visual field defects and hypothalamic-pituitary failure (11,12). The pathological diagnosis is performed surgically and complete or partial resection is often possible with advanced neurosurgical techniques.

Reports on the treatment and long-term outcomes for patients with suprasellar germinomas, in particular, are rare. The optimal treatment for suprasellar germinomas and NGGCTs remains an open question and studies on survival or factors that may predict better or worse outcomes for patients with these relatively rare tumors are sparse. In this study, we aimed to retrospectively review cases of pathologically confirmed suprasellar GCTs treated with surgery followed by radiotherapy, with or without chemotherapy, at a single institution. Our goal was to identify factors predictive of overall

Table I. Patient characteristics and hazard ratios from univariate analyses for overall and progression-free survival.

		Univariate analysis		
Variables	No. of patients	Hazard ratio	95% confidence interval	P-value
Gender				
Male	9	0.470	(0.105-2.106)	0.324
Female	14			
Age (years)				
<10	1	0.964	(0.848-1.095)	0.570
10-20	12			
21-30	9			
>30	1			
Lesion size (cm)				
2-4	17	12.183	(2.230-66.571)	0.004
>4	6			
Extent of surgical resection				
Total or subtotal resection	6	2.422	(0.291-20.161)	0.413
Partial resection or biopsy	17			
Pathological classification				
Pure germinoma	18	8.500	(1.848-39.099)	0.006
Mixed germ cell tumor	5			
Radiotherapy technique				
Whole-brain + boost	6	0.827	(0.159-4.295)	0.821
Craniospinal + boost	17			
Radiation dose (Gy)				
<50	6	0.316	(0.094-1.058)	0.062
50-55	12			
>55	5			
Combined modality therapy				
Radiochemotherapy	9	0.966	(0.216-4.334)	0.966
Radiotherapy	14			
Response to therapy				
Complete	15	3.392	(0.752-15.301)	0.112
Partial	8			

survival (OS) and progression-free survival (PFS) in such cases.

Materials and methods

Clinical data. We retrospectively identified 23 consecutive patients with suprasellar GCT treated at a single institution between April, 1987 and October, 2008. All the patients had undergone exploratory craniotomy with tumor resection and the diagnosis of GCT was pathologically confirmed according to the criteria of the World Health Organization (13). Computed tomography (CT) and magnetic resonance imaging (MRI) were used prior to radiochemotherapy to confirm the absence of lesions outside the suprasellar region. The tumors of 5 patients had NGGCT components (2 with immature teratoma and embryonal carcinoma, 1 with embryonal carcinoma, 1 with mature teratoma and 1 with immature teratoma). The median age of the 23 patients (9 male and 14 female) was 20 years (range, 9-34 years). The patient characteristics are summarized in Table I.

Radiotherapy. All 23 patients underwent postoperative radiotherapy; 17 patients (13 with pure germinoma and 4 with mixed GCT) received craniospinal irradiation (CSI) and 6 patients received whole-brain radiotherapy (WBRT), followed by a boost dose to the primary tumor bed. Prior to 1995, radiation was delivered from a cobalt-60 source, whereas linear accelerators were used from 1995 onwards [Varian 2100CD (1995-2008) and Siemens PRIMUS accelerator (2004-2008)]. The dose range delivered via WBRT was 28-34 Gy (median, 32 Gy) and that delivered by CSI was 17.6-34.2 Gy (median, 27.6 Gy); all radiation doses were delivered in 1.6- to 2.0-Gy fractions, 5 fractions per week. A total of 3 patients received three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiation therapy (IMRT) as a boost to the tumor bed and 20 patients

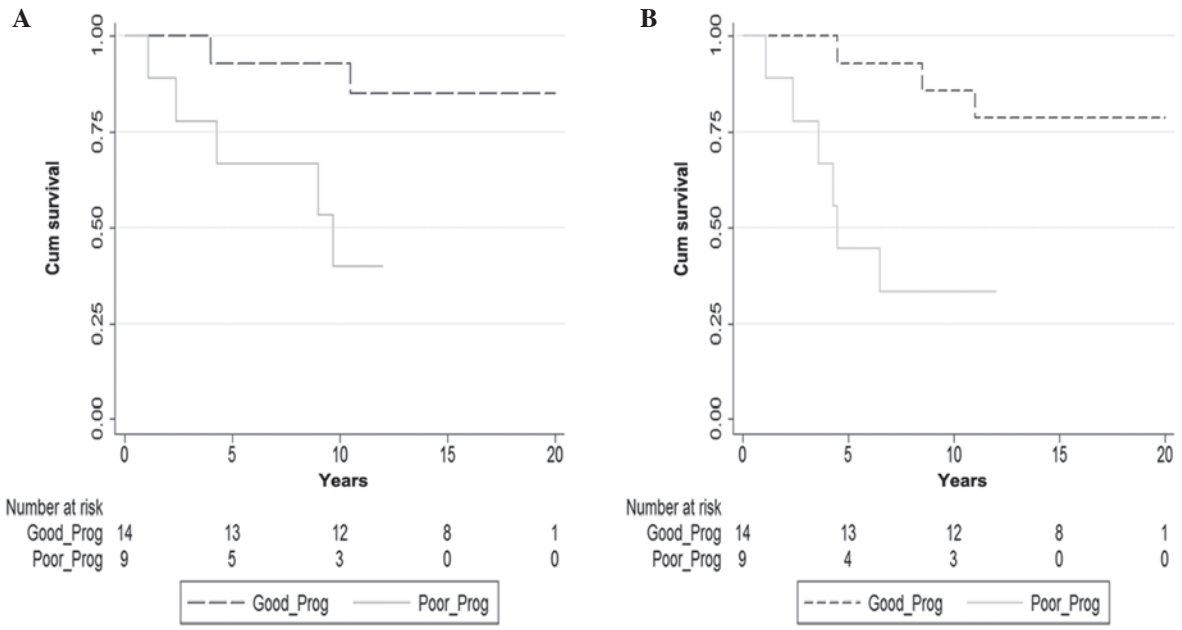

Figure 1. (A) Overall and (B) progression-free survival rates according to prognostic group. The numbers below the years indicate the numbers of patients at risk of death in each group.

received a local boost by conventional radiotherapy (boost dose to the tumor bed of 10-34 Gy, in 2-Gy fractions; median dose, 23.3 Gy). The range of total doses to the tumor bed was 39.6-56.8 Gy and the median dose was 51.9 Gy.

Chemotherapy. A total of 9 patients (7 with pure germinoma and 2 with mixed GCTs) received chemotherapy (range, 2-6 cycles); 6 patients received CSI and chemotherapy. All the patients received intravenous cisplatin 30 mg/m^2/day for 3 days every 3-4 weeks; 6 patients also received nimustine 2-3 mg/kg/day for 1 day every 6 weeks and 3 received cisplatin plus the podophyllotoxin derivative teniposide 100 mg/day for 3 days every 3-4 weeks.

Assessment of treatment. The extent of surgical resection was estimated from enhanced CT or MRI scans obtained prior to and again typically 3 days after neurosurgery (the standard protocol at the study institution). The patients were allocated total, subtotal and partial resection or biopsy procedures. Total resection was defined as complete removal of the visible tumor, subtotal resection indicated a >90% volume reduction, partial resection involved a 50-90% volume reduction and biopsy indicated a <50% volume resection. The responses to therapy were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, version 1.1 (14) as follows: complete response, disappearance of all target lesions; partial response (PR), ≥30% decrease in the sum of diameters of target lesions; progressive disease (PD), ≥20% increase in the sum of diameters of target lesions; and stable disease, neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Follow-up examinations following completion of radiotherapy and/or chemotherapy were performed by CT or MRI every 3 months in the first year, once every 6 months from the second to the third year following completion of treatment and at 1-year intervals thereafter.

Statistical analyses. Survival analyses were performed with the Stata v10.0 software package (StataCorp, College Station, TX, USA). A Cox proportional hazards model was used for univariate analyses to identify factors predictive of survival; the variables entered in the univariate analysis were patient gender, age, lesion size, extent of surgical resection, pathological classification (pure germinoma or mixed GCT), radiotherapy technique used, radiation dose received, chemotherapy administration and response to therapy. Forward selection was used to introduce variables into the Cox proportional hazards model. $P<0.05$ was considered to indicate statistically significant differences. The results of the Cox proportional hazard analyses were used to assign patients into good-prognosis or poor-prognosis groups. The Kaplan-Meier method was used to estimate OS and PFS rates at 5 and 10 years for each prognostic group and log-rank tests were used to identify differences between the groups. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient outcome. The median follow-up time was 12.3 years (range, 1.1-20.0 years). One patient was lost to follow-up after 12.5 years. The OS rates for all 23 patients were 82.6% at 5 and 72.9% at 10 years. A total of 4 patients succumbed to recurrent disease as follows: 1 patient developed recurrence at the primary site 1.2 years after radiochemotherapy; re-irradiation with local-field radiotherapy at that time achieved a PR and the patient eventually succumbed to the disease 3.1 years after the re-irradiation. The second patient developed recurrent disease in the left basal ganglia and spinal cord after radiotherapy, which was treated with salvage chemotherapy; the patient died during chemotherapy 1.1 years after the radiotherapy. The third patient experienced metastasis in the left orbit 3.5 years after WBRT plus partial brain irradiation; at that time, the left orbit was treated with 30 Gy and the patient succumbed to

the disease 2 years after the re-irradiation. The fourth patient experienced multiple metastases in the pineal region, right temporal lobe and lateral ventricle, declined further treatment and succumbed to disseminated disease 9.7 years after the radiochemotherapy.

Survival analysis. The univariate analysis of Cox proportional hazards model revealed that two factors affected survival rates, namely lesion size (2-4 vs. >4 cm) and pathological classification (pure germinoma vs. mixed GCT) (Table I). Based on the results of this analysis, all the patients were assigned to either a good-prognosis group (n=14, lesions 2-4 cm and pure germinomas) or a poor-prognosis group (n=9, lesions >4 cm and mixed GCTs). The OS rates at 5 and 10 years were both 92.9% in the good-prognosis group; the corresponding OS rates for the poor-prognosis group were 66.7 and 40.0% (P=0.020) (Fig. 1A). The PFS rates at 5 and 10 years in the good-prognosis group were 92.9 and 85.7%; the corresponding PFS rates in the poor-prognosis group were 44.4 and 33.3% (P=0.007) (Fig. 1B)

Discussion

The key findings from our study may be summarized as follows: Tumor size and pathological subtype (pure germinoma vs. mixed GCT) were the only factors that distinguished patients with good from those with poor survival outcomes following adjuvant radiotherapy or radiochemotherapy for suprasellar GCTs. These factors were significant for both OS and PFS.

Previous reports on the survival rates for patients with suprasellar germinoma have been somewhat sparse and the majority involved small numbers of subjects and tumors of different histologies treated with different types of therapy. A 1978 study of 16 patients with biopsy-confirmed suprasellar germinoma treated with surgical decompression and relatively high-dose radiotherapy to the primary site reported a 5-year survival rate of 77% (15). Our 5-year OS rate of 82.6% for all patients was higher compared to that value, but lower compared to the results of other studies, which may reflect the inclusion of 5 patients with mixed GCTs in our study, who typically have a worse prognosis than germinomas. Indeed, Jaing *et al* (4) reported projected 5-year OS and event-free rates of 92.6 and 92.6%, respectively, for 27 patients with germinomas vs. 47.3 and 42.1%, respectively, for 17 patients with NGGCTs; in addition, Hoffman *et al* (12) reported 5-year OS rates of 85.1% for 25 patients with germinomas and 45.5% for 13 patients with NGGCTs. Other groups, when attempting to rank subtypes of NGGCTs in terms of good, intermediate (immature teratoma, teratoma with malignant transformation and mixed tumors with a main component of germinoma or teratoma) and poor prognosis (other highly malignant tumors), observed that survival rates were worse in the poor-prognosis group compared to those in the other two groups (16,17). These findings were similar to ours.

Several groups have reported that only tumor histology predicts outcome for tumors in the pineal region (i.e., NGGCTs), whereas patient age, gender, type of surgical procedure, radiotherapy field and tumor dose do not. The same groups have also reported that definitive radiotherapy may control germinomas, but that a more aggressive approach is required for local control of NGGCTs; they further recommend that WBRT or CSI be considered for locally advanced tumors (4,18,19). In one review of 32 patients with NGGCT, tumor histology and the use of CSI predicted relapse-free survival and CSI was found to be significantly associated with OS. The authors of that review concluded that combined-modality therapy including surgery, radiotherapy and chemotherapy was effective for treating NGGCTs and that CSI should be considered for patients with highly malignant non-teratoma NGGCTs, as most treatment failures in that group occurred in the cerebrospinal fluid (17). Indeed, another study reported that the administration of salvage CSI was the only significant factor in the multivariate analysis for predicting survival following recurrence of intracranial germinomas (P=0.03), concluding that CSI, with or without chemotherapy, may be an effective salvage strategy for disease that recurs following reduced-volume radiotherapy (20). Another study reported that large (≥4 cm) or multifocal intracranial disease were independent risk factors for spinal recurrence in intracranial germinoma, but that radiation fields, dose and use of chemotherapy did not predict spinal recurrence (21). Another univariate analysis of treatment outcomes in 84 patients with intracranial germinoma demonstrated that tumors sized <3 cm were associated with better prognosis, but that patient age, gender, tumor location, treatment volume, radiation dose to both the primary tumor and the spinal cord and the extent of surgical resection were not (22). Thus, there exists some controversy as to which factors predict survival for patients with intracranial germinoma. Our univariate analyses indicated that the only factors affecting OS and PFS were lesion size and pathological classification (P<0.05), findings that are consistent with most of the literature published to date. With the advent of 3D-CRT and IMRT, whole-ventricular irradiation (WVI) is increasingly used to treat intracranial germinomas. WVI administered as IMRT may spare significant amounts of normal CNS tissue compared to WVI administered as 3D-CRT or with WBRT for the treatment of CNS GCTs (23). Chen *et al* (24) reported that WVI with a primary boost without chemotherapy was sufficient for the treatment of non-disseminated intracranial germinomas, even with a lower primary radiation dose (<36 Gy). However, Khatua *et al* (25) and Paximadis *et al* (26) reported that neoadjuvant chemotherapy followed by reduced-dose WVI and local boost irradiation appeared to be effective for localized pure germinoma of the CNS.

In conclusion, as the outcomes for patients with NGGCTs in the suprasellar region are less favorable compared to those for patients with pure germinomas, we recommend that pathological confirmation be obtained for all suprasellar tumors, so that treatment selection may be guided by the pathological subtype. Indeed, several reports have indicated that the survival of patients with biopsy-confirmed intracranial germinomas was superior to that of unbiopsied patients with a presumptive diagnosis of germinoma (18,27). No standard treatment has been established for NGGCTs. Histological confirmation may help select the most effective treatment strategy and OS rates may be stratified by histological subtypes (28). As NGGCTs are refractory to conventional irradiation, radiotherapy alone is not recommended for NGGCTs. Chemotherapy in conjunction with postoperative radiotherapy may achieve better outcomes compared to radiation alone (12,29,30).

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References

1. Jia G, Luo SQ, Li CD and Ma ZY: Long-term effect of chemotherapy combined with radiotherapy in treatment of intracranial germinoma: report of 39 cases. Chin Med J 83: 198-200, 2003 (In Chinese).
2. Echevarria ME, Fangusaro J and Goldman S: Pediatric central nervous system germ cell tumors: a review. Oncologist 13: 690-699, 2008.
3. Wang HW, Wu YH, Hsieh JY, *et al*: Pediatric primary central nervous system germ cell tumors of different prognosis groups show characteristic miRNome traits and chromosome copy number variations. BMC Genomics 11: 132, 2010.
4. Jaing TH, Wang HS, Hung IJ, *et al*: Intracranial germ cell tumors: a retrospective study of 44 children. Pediatr Neurol 26: 369-373, 2002.
5. Huh SJ, Shin KH, Kim IH, Ahn YC, Ha SW and Park CI: Radiotherapy of intracranial germinomas. Radiother Oncol 38: 19-23, 1996.
6. Aoyama H, Shirato H, Kakuto Y, *et al*: Pathologically-proven intracranial germinoma treated with radiation therapy. Radiother Oncol 47: 201-205, 1998.
7. Ogawa K, Shikama N, Toita T, *et al*: Long-term results of radiotherapy for intracranial germinoma: a multi-institutional retrospective review of 126 patients. Int J Radiat Oncol Biol Phys 58: 705-713, 2004.
8. Shim KW, Kim TG, Suh CO, *et al*: Treatment failure in intracranial primary germinomas. Childs Nerv Syst 23: 1155-1161, 2007.
9. Eom KY, Kim IH, Park CI, *et al*: Upfront chemotherapy and involved-field radiotherapy results in more relapses than extended radiotherapy for intracranial germinomas: modification in radiotherapy volume might be needed. Int J Radiat Oncol Biol Phys 71: 667-671, 2008.
10. Cho J, Choi JU, Kim DS and Suh CO: Low-dose craniospinal irradiation as a definitive treatment for intracranial germinoma. Radiother Oncol 91: 75-79, 2009.
11. Jennings MT, Gelman R and Hochberg F: Intracranial germ-cell tumors: natural history and pathogenesis. J Neurosurg 63: 155-167, 1985.
12. Hoffman HJ, Otsubo H, Hendrick EB, *et al*: Intracranial germ-cell tumors in children. J Neurosurg 74: 545-551, 1991.
13. Rychly B, Sidlova H and Danis D: The 2007 World Health Organisation classification of tumours of the central nervous system, comparison with 2000 classification. Cesk Patol 44: 35-36, 2008 (In Slovak).
14. Eisenhauer EA, Therasse P, Bogaerts J, *et al*: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247, 2009.
15. Sung DI, Harisiadis L and Chang CH: Midline pineal tumors and suprasellar germinomas: highly curable by irradiation. Radiology 128: 745-751, 1978.
16. Kanamori M, Kumabe T, Saito R, *et al*: Optimal treatment strategy for intracranial germ cell tumors: a single institution analysis. J Neurosurg Pediatr 4: 506-514, 2009.
17. Kim JW, Kim WC, Cho JH, *et al*: A multimodal approach including craniospinal irradiation improves the treatment outcome of high-risk intracranial nongerminomatous germ cell tumors. Int J Radiat Oncol Biol Phys 84: 625-631, 2012.
18. Chao CK, Lee ST, Lin FJ, Tang SG and Leung WM: A multivariate analysis of prognostic factors in management of pineal tumor. Int J Radiat Oncol Biol Phys 27: 1185-1191, 1993.
19. Wolden SL, Wara WM, Larson DA, Prados MD, Edwards MS and Sneed PK: Radiation therapy for primary intracranial germ-cell tumors. Int J Radiat Oncol Biol Phys 32: 943-949, 1995.
20. Hu YW, Huang PI, Wong TT, *et al*: Salvage treatment for recurrent intracranial germinoma after reduced-volume radiotherapy: a single-institution experience and review of the literature. Int J Radiat Oncol Biol Phys 84: 639-647, 2012.
21. Ogawa K, Yoshii Y, Shikama N, *et al*: Spinal recurrence from intracranial germinoma: risk factors and treatment outcome for spinal recurrence. Int J Radiat Oncol Biol Phys 72: 1347-1354, 2008.
22. Shibamoto Y, Takahashi M and Abe M: Reduction of the radiation dose for intracranial germinoma: a prospective study. Br J Cancer 70: 984-989, 1994.
23. Chen MJ, Santos Ada S, Sakuraba RK, *et al*: Intensity-modulated and 3D-conformal radiotherapy for whole-ventricular irradiation as compared with conventional whole-brain irradiation in the management of localized central nervous system germ cell tumors. Int J Radiat Oncol Biol Phys 76: 608-614, 2010.
24. Chen YW, Huang PI, Ho DM, *et al*: Change in treatment strategy for intracranial germinoma: long-term follow-up experience at a single institute. Cancer 118: 2752-2762, 2012.
25. Khatua S, Dhall G, O'Neil S, *et al*: Treatment of primary CNS germinomatous germ cell tumors with chemotherapy prior to reduced dose whole ventricular and local boost irradiation. Pediatr Blood Cancer 55: 42-46, 2010.
26. Paximadis P, Hallock A, Bhambhani K, *et al*: Patterns of failure in patients with primary intracranial germinoma treated with neoadjuvant chemotherapy and radiotherapy. Pediatr Neurol 47: 162-166, 2012.
27. Kersh CR, Constable WC, Eisert DR, *et al*: Primary central nervous system germ cell tumors. Effect of histologic confirmation on radiotherapy. Cancer 61: 2148-2152, 1988.
28. Sawamura Y: Current diagnosis and treatment of central nervous system germ cell tumours. Curr Opin Neurol 9: 419-423, 1996.
29. Kochi M and Ushio Y: Chemo-radiotherapy for malignant brain tumors. Cancer & chemotherapy 29: 669-676, 2002 (In Japanese).
30. Matsutani M: Pineal germ cell tumors. Prog Neurol Surg 23: 76-85, 2009.