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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Treatment outcomes of intracranial germinoma: a retrospective analysis of 170 patients from a single institution

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Abstract

Purpose To perform a retrospective analysis of patients with intracranial germinoma treated in our department to evaluate treatment outcomes and determine optimal treatment strategies.

Methods We reviewed the treatment outcomes of 170 patients with intracranial germinoma who were treated in our department from January 1996 to January 2017. The median patient age was 15 years old. Among the patients, 56 (33%) were pathologically diagnosed, and 114 (67%) were diagnosed clinically. Various radiation fields and doses were used. Cerebrospinal fluid (CSF) and serum beta-human chorionic gonadotropin (β-HCG) levels were examined before treatment in 114 patients. Endocrinological evaluation was performed in 141 patients before and after treatment. A total of 38 patients received chemotherapy prior to radiotherapy (RT). The median follow-up time was 64.5 months (range 4–260.5 months).

Results The 5- and 10-year overall survival (OS) rates were 94.5% and 91.3%, respectively. The relapse-free survival (RFS) rates at 5- and 10-years were 91.9% and 78.1%, respectively. Relapses occurred in 18 patients within 6 months–10 years. The spinal cord metastasis rate was 3.4% in patients with a localized lesion who did not receive spinal cord irradiation and 16.7% in patients with bifocal disease who were treated using whole ventricular irradiation (WVI) or whole brain radiotherapy (WBRT). Treatment failure did not occur in patients receiving chemoradiotherapy or in patients receiving three-dimensional conformal radiation therapy (3D-CRT)/intensity-modulated radiation therapy (IMRT). The RFS rate did not have a statistically significant correlation with the CSF/serum β-HCG level. After RT, 19.1% of the patients developed newly impaired pituitary function and required hormone replacement therapy.

Conclusions WVI or WBRT+primary boost (PB) is a sufficient irradiation field for localized intracranial germinoma, while patients with bifocal disease should undergo craniospinal irradiation (CSI), especially when treated with RT alone. CSF β-HCG is not a prognostic marker for intracranial germinomas. The treatment results of chemotherapy followed by reduced-dose RT are comparable to those of RT alone. IMRT is recommended for intracranial germinoma to improve the target volume accuracy and decrease the complications of RT.

Keywords CNS tumor · Germinoma · Radiotherapy · Pediatric tumor

Introduction

Intracranial germ cell tumors are a rare malignant disease of the central nervous system and have a variety of histological classifications. Germinomas constitute approximately two-thirds of all intracranial germ cell tumors. The incidence of germinomas has been considered to be higher in East Asia than in Western countries, but a recent study has shown that the incidence of these tumors is similar between Japan and the United States (0.096/100000/year and 0.075/100000/year, respectively). Intracranial germinomas most commonly occur in childhood and adolescence, with 35–40% of cases occurring before the age of 14 years and 90% of patients diagnosed before the age of 20 years (McCarthy et al. 2012). Intracranial germ cell tumors most commonly arise in the pineal gland, suprasellar region and basal ganglia, sometimes presenting as a bifocal disease (synchronous

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suprasellar and pineal tumors), and in rare cases are diagnosed as germinoma with disseminated disease (Chen et al. 2012b; Weksberg et al. 2012). An intracranial germinoma is sensitive to both radiotherapy (RT) and chemotherapy, and these patients have excellent long-term survival; therefore, we should be more concerned about the late effects of RT, especially in affected children. In the current study, we reviewed 170 patients with intracranial germinoma treated in our single institution to evaluate the treatment results and to discuss treatment strategies.

Materials and methods

Patient characteristics

We analyzed 170 patients with intracranial germinoma treated in our department from January 1996 to January 2017. Of these, 94 patients were male, and 76 were female, with a median age of 15 years (range 4–39 years). Clinical symptoms included central diabetes insipidus, hypopituitarism, ophthalmic abnormality, sex precocity, obstructive hydrocephalus and motor dysfunction. All the patients underwent magnetic resonance imaging (MRI) to define the tumor and its extent before treatment. Among the 170 patients, there were 103 cases of localized disease (95 in the sellar and suprasellar regions, 2 in the pineal gland and 6 in the region of the basal ganglia), 47 cases of bifocal disease and 20 cases of disseminated disease (macroscopic or microscopic). A total of 56 (33%) patients were diagnosed pathologically, while 114 (67%) were diagnosed clinically based on the clinical characteristics. A clinical diagnosis in our institution was made using the following parameters: an age younger than 40 years; a typical tumor location on MRI; no elevation in the cerebrospinal fluid (CSF)/serum AFP level; and a rapid response to RT with more than an 80% reduction in the maximum diameter at a dose of 20 Gy delivered in 10 fractions. We examined the beta-human chorionic gonadotropin (β-HCG) level in serum and CSF samples before treatment in 114 patients. An endocrinological evaluation was performed in 141 patients before and after treatment. A total of 38 patients received chemotherapy prior to RT. The patient characteristics are summarized in Table 1.

Radiotherapy

All the patients received linear accelerator RT. Prior to 2012, 103 patients were treated with conventional RT, and after that, three-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiation therapy (IMRT) were used to treat 67 patients. The RT fields included local fields ($n = 2$), whole ventricular irradiation (WVI) plus

Table 1 Patient characteristics

Characteristics	Total $n = 170$	Clinical $n = 114$	Pathological $n = 56$
Gender			
Male	94	71	23
Female	76	43	33
Median age (years)	15 (range 4–39)	15 (range 4–37)	14 (range 7–39)
Tumor location			
Local lesion	103	68	35
Sellar and suprasellar	95	63	32
Pineal	2	0	2
Basal ganglion	6	5	1
Bifocal disease	47	34	13
Dissemination	20	12	8
Clinical symptoms			
Diabetes insipidus	160	108	52
Ophthalmic abnormalities	25	14	11
Hypopituitarism	109	65	44
Sex precocity	3	0	3
Obstructive hydrocephalus	10	8	2
Motor dysfunctions	12	8	4
CSF β-HCG (U/L)	114		
≤5	42	24	18
5–100	61	33	28
>100	11	7	4

primary boost (PB) ($n=82$), whole brain radiotherapy (WBRT) plus PB ($n=32$) and craniospinal irradiation (CSI) plus PB ($n=54$). The relationship between the radiation field and tumor location is summarized in Table 2. In the conventional RT, WBRT and WVI were performed using two opposed lateral fields, and a local field was formed using two opposed lateral fields and an anterior field, whereas a spinal field was accomplished using posterior–anterior vertical irradiation. When 3D-CRT and IMRT were used, CT simulation was performed, and target volume delineation was required. The clinical target volume (CTV) for WVI was defined as the whole ventricular system (including the bilateral lateral ventricles and the third and fourth ventricles, along with the suprasellar cistern) plus a margin of 0.8–1 cm, and the CTV for WBRT was defined as the whole cranial content. The CTV for CSI often included the sum of the whole brain and the entire spinal canal down to the end of the thecal sac. The PB field was generally defined as the primary tumor with a margin of 1 cm. The RT dose to the primary site ranged from 29 to 52 Gy (median, 45 Gy), and the prophylactic dose to the whole ventricle, whole brain and spinal cord ranged from 19.8 to 36 Gy (median, 25 Gy). When patients received chemoradiotherapy, the RT dose was reduced to 30–40 Gy (median, 36 Gy) and 17.8–25 Gy (median, 20 Gy) to the primary site and the prophylactic area, respectively, for patients who achieved complete remission (CR) with chemotherapy.

Chemotherapy

A total of 38 of the 170 patients with pathologically proven germinomas received chemoradiotherapy. The chemotherapy was mainly a platinum-based regimen for 1–6 cycles; 32 patients received cisplatin + etoposide, and the other patients received ifosfamide + cisplatin + etoposide. We evaluated the response to chemotherapy after 3–4 cycles and before initiating the RT. CR was determined if none of the lesions were visible on MRI and the positive cytology became negative. A partial remission (PR) was defined as a tumor volume decrease of ≥ 50% of the pretreatment volume or the absence of visible lesions on MRI but with positive cytology. If the patients had a CR, reduced-dose RT was performed.

Treatment outcomes evaluation, follow-up and statistical analysis

We usually suggested that patients be followed up at 6-month intervals until 5 years after the completion of treatment and at 1-year intervals thereafter. Evaluations of the tumor response on MRI and tumor markers in the CSF/serum and an endocrinological assessment were performed during the follow-up visits. A relapse was defined as the radiographic appearance of a new tumor in patients who had previously achieved a CR. Relapse-free survival (RFS) was defined as the time from the first day of RT to the day of any evidence of relapse or to the last follow-up day if the patient was alive with no documented recurrence. Overall survival (OS) was defined as the time from the first day of RT to the date of a patient's death or the last follow-up visit. Curves for the RFS and OS were generated using the Kaplan–Meier method and were compared using the log-rank test. The median follow-up time for all the patients was 64.5 months (range 4–260.5 months), and 32 (22%) patients were followed up for more than 10 years.

Results

Treatment outcomes and patterns of failure

The 5- and 10-year OS rates were 94.5% and 91.3%, respectively. The RFS rates at 5- and 10-years were 91.9% and 78.1%, respectively (Fig. 1). There was no statistically significant difference between cases with a clinical diagnosis and those with a pathological diagnosis in 5-year OS (94.1% vs 95.7%, $p=0.300$) or RFS (90.9% vs 95.3%, $p=0.704$).

Ten of the 170 patients died. One 5-year-old child died of hypothalamic dysfunction 6 months after RT, and 1 patient died of misinhalation when he received retreatment due to recurrence in the fourth ventricle. The remaining 8 patients died from this disease. Relapse occurred in 18 patients; 10

Table 2 Tumor location and RT fields

	Local ($n=2$)	WVI + PB ($n=82$)	WBRT + PB ($n=32$)	CSI + PB ($n=54$)	Total ($n=170$)
Sellar and suprasellar	2	74	8	11	95
Pineal	0	1	0	1	2
Basal ganglion	0	0	6	0	6
Bifocal	0	7	16	24	47
Dissemination	0	0	2	18	20

CSI craniospinal irradiation, *PB* primary boost, *WBRT* whole brain radiotherapy, *WVI* whole ventricular irradiation

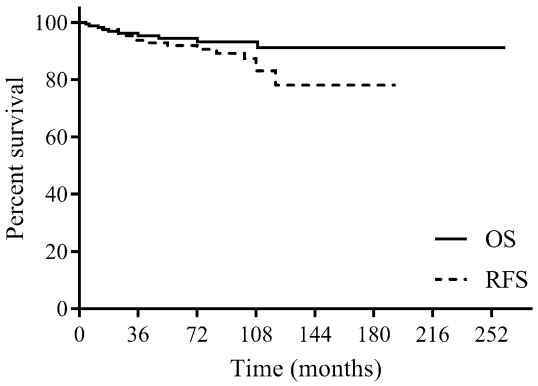

Fig. 1 Relapse-free survival (RFS) and Overall survival (OS) for all patients (N = 170)

patients had intracranial recurrences, and 8 patients developed spinal cord metastases. The time to the diagnosis of a relapse after primary treatment was from 6 months to 10 years.

The following results were found for the 103 patients with a localized lesion: 1 patient who was treated with a local field developed an intracranial recurrence; 5 intracranial recurrences and 1 spinal cord metastasis were found in the WVI + PB group; 2 spinal metastases were found in the WBRT + PB group; and 1 intracranial recurrence was found in the CSI + PB group. Of the 47 patients with bifocal disease, 3 intracranial recurrences and 1 spinal cord metastasis were found in the WVI + PB group, and 3 spinal cord metastases were found in the WBRT + PB group. Among the 20 patients with disseminated disease, 1 spinal cord metastasis was found in the WBRT + PB group. The relationship between the radiation field and relapse site is summarized in Table 3. An "in-field" recurrence was found in only 2 patients. The RT dose to the tumor in these two cases was 37.8 Gy and 44 Gy, respectively. All 18 relapsed patients were treated with conventional RT.

Tumor marker and treatment outcomes

The CSF/serum β-HCG and AFP levels were examined in 114 patients. The CSF β-HCG level ranged from 0.6 to 2313 U/L (median, 7 U/L), and CSF β-HCG levels of ≤ 5 U/L, 5–100 U/L and > 100 U/L were found in 11 (9.6%), 61 (53.5%) and 42 (36.8%) patients, respectively. In these three groups, there were 2, 1 and 1 relapsed patients, respectively. There was no statistically significant difference in the RFS of these groups ($p = 0.527$). The serum β-HCG level ranged from 0 to 1220 U/L (median, 0.75 U/L) and was always lower than the corresponding level in the CSF. The serum β-HCG level also showed no statistically significant correlation with the RFS. None of the patients had an elevated AFP level in the CSF or serum.

Table 3 Radiation fields and relapse sites

	Local	WVI + PB	WBRT + PB	CSI + PB	Total
Local lesion					
Relapse (total)	1 (2)	6 (75)	2 (14)	1 (12)	10 (103)
In brain	1	5	0	1	7
In spinal	0	1	2	0	3
Bifocal disease					
Relapse (total)	–	4 (7)	3 (16)	0 (24)	7 (47)
In brain	–	3	0	0	3
In spinal	–	1	3	0	4
Dissemination					
Relapse (total)	–	–	1 (2)	0 (18)	1 (20)
In spinal	–	–	1	0	1

CSI craniospinal irradiation, *PB* primary boost, *WBRT* whole brain radiotherapy, *WVI* whole ventricular irradiation

Chemoradiotherapy results

Since 2012, 38 patients were treated with chemoradiotherapy, and 35 of these patients completed 3–6 cycles of chemotherapy. Eleven of these patients had a PR to chemotherapy, and 24 patients had a CR. The other 3 patients received chemotherapy for only 1–2 cycles because of the development of abnormal hepatic function and serious myelosuppression. Among the 11 PR patients, 3 had tumor lesions located in the region of the basal ganglia, 1 had a cyst-like lesion, and 1 had a small enhanced sellar lesion visible on MRI until 14 months after RT. The patient with the small persistent lesion underwent surgery, and her pathology was found to be a mature teratoma. None of the 38 patients who had chemoradiotherapy experienced treatment failure.

Assessment of complications

We evaluated pituitary functions, including the hypothalamus–pituitary–adrenal (HPA) axis, the hypothalamus–pituitary–thyroxine (HPT) axis, the hypothalamus–pituitary-gonad (HPG) axis and growth hormone (GH), for 141 of the 170 patients before and after RT. Of these, 122 (86.5%) patients had at least one pituitary hormone deficiency before RT. Pituitary functions were reevaluated each time the patients returned to the hospital for review after treatment. We found that 27 (19.1%) of the 141 patients developed newly impaired pituitary function after RT that required hormone replacement therapy.

We evaluated the neurocognitive function of 119 patients based on whether the patients could return to and complete school or experienced memory deterioration and became candidates for general social work. Twenty patients

experienced a decline in neurocognitive function; 7 of these had been treated with WVI, and 13 had been treated with WBRT or CSI. The tumor dose was above 40 Gy in all 20 patients.

Discussion

An intracranial germinoma is a curable malignant CNS tumor, and RT alone can achieve excellent results with an OS rate of more than 90% at 10 years. We found that the treatment outcome was similar to that reported in many previous studies (Chen et al. 2012a; Haas-Kogan et al. 2003; Kanamori et al. 2009; Ogawa et al. 2004; Schoenfeld et al. 2014; Shim et al. 2007). Historically, since there is a high risk of operative morbidity and mortality, a therapeutic irradiation trial has been used as an alternative diagnostic measure (Nakagawa et al. 1992). Most of our patients were clinically diagnosed, but their treatment results were similar to those of the pathologically diagnosed patients.

In our study, 10 patients with suprasellar localized lesions relapsed. Among them, 2 patients received local field irradiation. This treatment led to 1 recurrence in the brain. This high failure rate has been demonstrated by many previous articles. The study of Aoyama et al. (1998) has shown that even with information from CT images, the use of a local irradiation field without including the ventricles is associated with a 10-year RFS rate as low as 22%. Kanamori et al. (2009) also reported superior 5- and 10-year progression-free survival (PFS) rates for patients in a WVI/WBRT/CSI-treated group relative to those in a local field-treated group. Because of the risk of spreading into the CSF, a local field is associated with a high relapse rate. However, although CSI yields excellent results, the risk of failure in the spinal cord may be overestimated in patients with localized lesions. In our study, 3 (3.4%) of 89 patients with a localized lesion who did not undergo spinal irradiation had metastasis to the spinal cord. Rogers et al. (2005) reviewed multiple studies and concluded that in patients with localized intracranial germinomas, the frequency of isolated spinal relapses did not differ significantly between patients treated with WVI + PB or WBRT + PB and those treated with CSI (2.9% vs 1.2%). Therefore, most experts no longer advocate the use of CSI in treating localized germinomas (Chen et al. 2012a; Ogawa et al. 2008; Shim et al. 2007).

Bifocal disease accounts for 2–41% of intracranial germinomas (Lafay-Cousin et al. 2006; Weksberg et al. 2012) and accounted for 27.6% (47 patients) in our study. The optimal RT field for bifocal disease remains controversial because bifocal disease is regarded as a metastatic disease in the USA and as localized disease in Europe (Rogers et al. 2005). Both arguments are supported by some clinical data. In Taiwan, Huang et al. (2008) treated 7 patients with bifocal disease using a WVI field, and no treatment failure was found with a median follow-up time of 49 months. Al-Mahfoudh et al. (2014) reviewed the literature and found that bifocal germinoma with no evidence of dissemination might obviate the need for CSI. However, Ogawa's study (Ogawa et al. 2008) had 18 patients with bifocal disease treated without a spinal irradiation field, and 3 (17%) of the patients experienced spinal cord metastases. In our study, 23 patients with bifocal disease treated with CSI did not experience a spinal cord failure, but 4 (16.7%) of the 24 patients treated using WVI or WBRT developed spinal cord metastases. Therefore, we have the same opinion as that of Ogawa et al., i.e., bifocal germinoma has some potential for metastasis, and we suggest that this type of germinoma should be treated with CSI.

The purpose of using chemoradiotherapy is to reduce the RT dose for those patients with a CR to chemotherapy with the goal of decreasing the complications of RT, especially in children and adolescents. It has been demonstrated that chemotherapy without RT is unable to cure intracranial germinomas. Kanamor et al. (2009) reported in a long-term follow-up study that treating 9 patients with chemotherapy alone led to PFS rates of 33% and OS rates of 88% at 5 years, and that of 33% and 70% at 10 years, respectively. These results are far worse than RT alone. However, the initial response rate to chemotherapy is high. Khatua's results (Khatua et al. 2010) demonstrated that 75% of patients achieved a greater than 90% response after two cycles and 95% after four cycles. Chemotherapy followed by low-dose RT, can achieve treatment results comparable to those obtained with a higher dose of RT alone. Many studies have reported that it is safe to reduce the RT dose to 30–40 Gy (Calaminus et al. 2013; Khatua et al. 2010; Shim et al. 2013). In chemoradiotherapy, local field irradiation is also not recommended for localized germinomas. Joo et al. (2014) reported that in the CR group after chemotherapy, the 5-year RFS rate was 100% after WBRT/WVI and 70% after local RT ($p = 0.04$). The SFOP experience identified an excess of periventricular relapses when a local field of radiation was used in the combined management of germinomas, and ventricular field irradiation appeared to be a logical alternative to decrease the incidence of such relapses (Alapetite et al. 2010). However, whether bifocal disease still requires CSI after chemotherapy remains a question. The conclusion of Weksberg et al. (2012) was that in only patients with bifocal disease who had no evidence of dissemination, the omission of spinal irradiation appeared to be a reasonable approach when chemotherapy was used. Lafay-Cousin et al. (2006) also thought that chemotherapy and focal RT (involving the whole ventricular system) might be sufficient to provide excellent outcomes.

We performed reduced-dose RT for patients if the initial chemotherapy achieved a CR after 3–4 cycles, but we did not reduce the RT field. There was no treatment failure in any of

our patients treated with chemoradiotherapy, but a long-term follow-up is required. We found that in the patients treated with chemotherapy who achieved a PR, there was a predominance of tumor lesions located in the region of the basal ganglia. We considered that this result might be related to the observation that basal ganglia region germinomas always have atypical MRI presentations and no clear lesion margin. We noted that when patients receiving chemotherapy achieved a PR, these patients might have had some non-germinoma germ cell tumor (NGGCT) components in the tumor, such as the teratoma in one of our patients.

Similar to most previous studies (Ogawa et al. 2004; Schoenfeld et al. 2014; Shin et al. 2001; Utsuki et al. 2002), our results also did not show a relationship between the CSF/serum β-HCG level and RFS. This finding demonstrates that an elevated CSF β-HCG level just indicates the presence of a tumor with syncytiotrophoblastic giant cells (STGCs) and does not predict that the outcome will be worse than that for germinomas with normal HCG levels. Furthermore, a threshold level for CSF β-HCG has not been established for diagnosing intracranial germinomas (Murray et al. 2015). The most frequently used value for the normal upper limit of the CSF β-HCG level is 5 U/L, the same as that used in our institution. However, Tian et al. (2011) measured the levels in 201 male patients who had various types of neurological diseases, and a reference value of 1.009 U/L β-HCG in the CSF was established.

Hypopituitarism is usually regarded as a complication of RT for intracranial germinomas, but we should take note of the pituitary function before RT. We had 122 of 141 patients with hypopituitarism before RT because sellar and suprasellar lesions constituted a higher proportion of the total lesions. However, we found only 22 (19.1%) patients who developed a new kind of pituitary hormone hyposecretion after treatment. Ogawa et al. (2004) found that only 3% of patients needed new hormone replacement therapy after RT. Chen et al. (2012a) found that no newly diagnosed hormonal deficiencies were evident after treatment, and 21% of patients were able to reduce their hormone supplementation after the completion of all treatments.

We assessed the neurocognitive function of the patients by some subjective methods, as it is difficult to perform standardized measures before and after treatment in a retrospective study. Despite this challenge, the outcomes also showed a trend of a large target volume and high dose of RT being associated with a neurocognitive decline. In the research by O'Neil et al. (2011), all 20 patients treated with chemotherapy followed by a reduced dose and volume of irradiation had no decline over time indicated by any of the neurocognitive measures. Qi et al. (2012) have proven that VMAT increases the conformality and reduces the dose to the surrounding normal tissue compared with 3D-CRT and might thus result in a reduction in the negative impact on cognition, as measured by IQ tests in children with intracranial germinoma.

All 18 patients with treatment failure were treated using conventional RT, and 8 of them treated with a WVI + PB field relapsed in the margin of the ventricle. We reviewed these cases and found that it might not be sufficient to use a WVI field when using conventional RT due to the irregular and individual ventricle extent. Since 2012, we have treated all patients with intracranial germinoma using 3D-CRT or IMRT, and this approach can improve the target volume accuracy as well as spare the normal brain tissue from high-dose irradiation (Qi et al. 2012; Raggi et al. 2008). In the last 4 years, we have used tomotherapy for CSI, which provides a more homogeneous RT dose distribution and avoids the 'hot' or 'cold' points at the spinal field junctions.

Conclusions

RT is the main treatment for intracranial germinomas. Our study demonstrated once again that WVI/WBRT + PB is a sufficient irradiation field for localized intracranial germinoma, and we suggest that bifocal disease should still be treated with CSI, especially when using RT alone. CSF β-HCG is not a prognostic marker for intracranial germinomas. Chemotherapy followed by reduced-dose RT has treatment results that are comparable to those of RT alone. We recommend IMRT for intracranial germinoma to improve the target volume accuracy and decrease the complications of RT.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval This study was approved by the institutional review board at Peking Union Medical College Hospital (PUMCH) [Protocol number S-K553].

Informed consent Informed consent was obtained from each patient or his/her guardian prior to initiating the treatment.

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