pISSN 1598-2998, eISSN 2005-9256

Cancer Res Treat. 2020;52(4):1050-1058 https://doi.org/10.4143/crt.2020.437

Original Article Open Access

Comparison between Craniospinal Irradiation and Limited-Field Radiation in Patients with Non-metastatic Bifocal Germinoma

Bo Li, MD, PhD[1,2]
Wenyi Lv, MM[1]
Chunde Li, MD[3]
Jiongxian Yang, MD[4]
Jiajia Chen, MD[5]
Jin Feng, MD[1]
Li Chen, MD[1]
Zhenyu Ma, MD[3]
Youqi Li, MM[1]
Jiayi Wang, MM[1]
Yanwei Liu, MD, PhD[1]
Yanong Li, MM[1]
Shuai Liu, MD, PhD[1]
Shiqi Luo, MD[3]
Xiaoguang Qiu, MD[1,2]

**A list of author's affiliations appears at the end of the paper.*

Correspondence: Shiqi Luo, MD
Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, No. 119, South 4th Ring West Road, Fengtai District, Beijing 100070, China
Tel: 86-10-67098006
Fax: 86-10-67098006
E-mail: bjthlsq@protonmail.com

Co-correspondence: Xiaoguang Qiu, MD
Department of Radiation Oncology, Beijing Tiantan Hospital, Capital Medical University, No. 119, South 4th Ring West Road, Fengtai District, Beijing 100070, China
Tel: 86-10-59975582
Fax: 86-10-67098587
E-mail: qiuxiaoguang@bjtth.org

Received May 9, 2020
Accepted July 8, 2020
Published Online July 9, 2020

*Bo Li and Wenyi Lv contributed equally to this work.

Purpose

Whether craniospinal irradiation (CSI) could be replaced by limited-field radiation in non-metastatic bifocal germinoma remains controversial. We addressed the issue based on the data from our series and the literature.

Materials and Methods

Data from 49 patients diagnosed with non-metastatic bifocal germinoma at our hospital during the last 10 years were collected. The Pediatric Quality of Life Inventory 4.0 was used to evaluate health-related quality of life (HRQOL). Additionally, 81 patients identified from the literature were also analyzed independently.

Results

In our cohort, 34 patients had tumors in the sellar/suprasellar (S/SS) plus pineal gland (PG) regions and 15 in the S/SS plus basal ganglia/thalamus (BG/T) regions. The median follow-up period was 52 months (range, 10 to 134 months). Our survival analysis showed that patients treated with CSI (n=12) or whole-brain radiotherapy (WBRT; n=34) had comparable disease-free survival (DFS; p=0.540), but better DFS than those treated with focal radiotherapy (FR; n=3, p=0.016). All 81 patients from the literature had tumors in the S/SS+PG regions. Relapses were documented in 4/45 patients treated with FR, 2/17 treated with whole-ventricle irradiation, 0/4 treated with WBRT, and 1/15 treated with CSI. Survival analysis did not reveal DFS differences between the types of radiation field (p=0.785). HRQOL analysis (n=44) in our cohort found that, compared with S/SS+PG germinoma, patients with BG/T involvement had significantly lower scores in social and school domains. However, HRQOL difference between patients treated with CSI and those not treated with CSI was not significant.

Conclusion

In patients with non-metastatic bifocal germinoma, it is rational that CSI could be replaced by limited-field radiation. HRQOL in patients with BG/T involvement was poorer.

Key words

Germinoma, Bifocal germinoma, Radiotherapy, Quality of life

Introduction

Intracranial germinoma is a rare malignancy mostly identified in children and adolescents. The incidence varies substantially across the continents, with North American and international data showing overall incidence of 0.6/million/yr in United States, 1.0/million/yr in Europe, 1.7/million/yr in Korea, and 2.7/million/yr in Japan [1,2]. The sellar/suprasellar (S/SS), pineal gland (PG), and basal ganglia/thalamus (BG/T) regions are the most common areas in which germinoma occurs, accounting for 23%-35%, 37%-66%, and 0%-8% of cases, respectively [2-5].

Craniospinal irradiation (CSI) used to be the standard of care for patients with germinoma. Although more than 90% of patients show long-term disease control, toxicities related to CSI are still concerning [6,7]. Thus, many researchers explored the possibility of limited-field irradiation such as focal radiotherapy (FR), whole ventricular irradiation (WVI), or whole-brain radiotherapy (WBRT) [8-11]. The emerging results showed that, combined with chemotherapy, reduction in the radiation dose and/or radiation field did not compromise the long-term survival of patients with localized disease. Interestingly, in clinical practice, some rare patients had synchronous lesions involving two intracranial locations; these cases are called bifocal germinoma. As dissemination within the central nervous system is characteristic of germinoma, treatment of cases with bifocal involvement is a dilemma at the time of decision-making, especially for radiation field selection.

Some pioneer researchers addressed the issue of bifocal germinoma treatment on the basis of their experience, and indicated that extended-field radiation could be avoided, if there is no evidence of metastasis or dissemination [12-14]. However, due to the scarcity of the disease, few studies have compared the difference between the above-mentioned radiation fields. Thus, evidence is still required to clarify the issue.

Classically, bifocal germinoma refers to patients with synchronous lesions involving S/SS and PG regions. However, we also identified a number of patients who have synchronous lesions involving S/SS and BG/T regions (Fig. 1, S1 Fig.). In the current study, we grouped them under the concept of bifocal germinoma and analyzed them together. Radiation strategies for patients with bifocal germinoma at our institute have evolved over the decades. Both CSI and FR were treatment options in the early years until WBRT became the standard of care. Here, we retrospectively analyzed clinical data from 49 patients to examine the survival of patients treated with different radiation fields. Moreover, we also independently analyzed 81 patients from the literature. In addition, since the long-term health-related quality of life (HRQOL) is another important factor that should be weighted at the time of radiation field selection, these data were also included in our study.

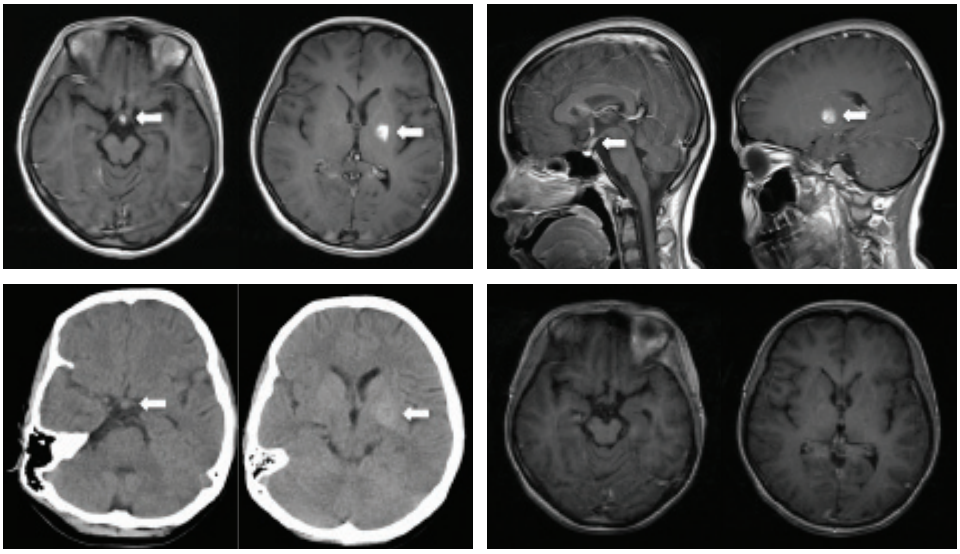

Fig. 1. Images of an 18-year-old girl who presented with right hemiparesis and adipsic diabetes insipitus. β-Human chorionic gonadotropin in the serum and cerebrospinal fluid was 39.4 IU/L and 77.2 IU/L, respectively. Radiological examinations revealed lesions located in the sellar and left thalamus area (tumors were indicated by the arrows). The first row shows axial and sagittal graphics on contrast-enhanced magnetic resonance image. Pituitary stalk enhancement and a left thalamus lesion with enhancement can be seen. The second row shows images on plain computed tomography scan. Lesions showed slightly higher intensity compared to the surrounding normal tissues. She was diagnosed as bifocal germinoma and chemoradiotherapy was applied. The third row shows the complete remission of the lesions after treatment.

Materials and Methods

1. Patients

Clinical data from 49 patients who were diagnosed with bifocal germinoma between January 2008 and January 2018 were analyzed. Diagnosis was established on the basis of histology and/or tumor makers (β-human chorionic gonadotropin [β-HCG] ≤ 100 IU/L and α-fetoprotein normal). Before treatment, all patients underwent baseline evaluation, including physical examination, blood tests, and radiographic examinations. Metastases were defined as any additional lesions documented on radiographic examinations and/or positive cerebrospinal fluid (CSF) cytology.

Considering the treatment strategy, two cycles of platinum-based chemotherapy (ifosfamide 1.5 g/m^2 days 1-3, etoposide 70 mg/m^2 days 1-3, and cisplatin 30 mg/m^2 days 1-3, repeated every 4 weeks) were initially performed after diagnosis. Subsequently, radiotherapy was applied and two additional cycles of chemotherapy were performed thereafter. The standard radiation dose in the current cohort was 40 Gy. In terms of radiation field at our institute, both FR and CSI (30 Gy) plus boosts had been considered for patients with bifocal disease, until WBRT (30 Gy) plus boost became the standard of care in 2008. Then, CSI plus boost was performed only in patients with evidence of metastases. Radiotherapy was applied at a daily dose of 1.6-1.8 Gy with five weekly fractions over 4.5-5 weeks. The gross target volume (GTV) was defined as the extent of the primary tumor(s) before treatment. The clinical target volume (CTV) was obtained by adding 0.5 cm to GTV. Additional 0.5-1 cm was added to CTV to create planning target volume (PTV). After treatment completion, routine follow-up was performed every 3-6 months for the first two years and every 6-12 months for the next 3 years.

2. Data from the literature

PubMed was used for literature searching. Patients who were eligible for the analysis must have information regarding diagnosis, tumor location, radiation field, radiation dose, chemotherapy, relapse status, and time to relapse. In addition, information about the age, sex, serum/CSF β-HCG level, CSF cytology results, and spinal magnetic resonance imaging (MRI) status were collected vigorously.

3. Health-related quality of life (HRQOL)

The Pediatric Quality of Life Inventory 4.0 (PedsQL 4.0) scale was used to evaluate HRQOL. The PedsQL 4.0 Generic Core Scale contains 23 items, which measure physical (eight items), emotional (five items), social (five items), and school functions (five items). HRQOL was provided as age-appropriate surveys for young children (5-7 years old), children (8-12 years old), teens (13-18 years old), young adults (18-25 years old), and adults (> 26 years old). The PedsQL 4.0 Generic Core Scale comprises parallel patient self-report and parent proxy-report formats. Items were reverse-scored and transformed to a 0-100 scale according to instructions, thus higher scores indicate better HRQOL. We attempted to contact all surviving patients via phone, and those who could be contacted received the electronic version of the PedsQL scale via e-mail and cell phone.

4. Statistical analysis

IBM SPSS Statistics for Windows, ver. 22.0 (IBM Corp., Armonk, NY), was used for data analysis. t test was employed for PedsQL scores analyses, which were considered as continuous variables. The Kaplan-Meier method was used to estimate survival. Disease-free survival (DFS) was calculated from the date of complete remission to the date of disease relapse. Disease relapse was defined as an elevation of tumor marker levels in the serum and/or CSF, the appearance of any new lesions on radiographic examinations, or both. Overall survival (OS) was determined from the date of diagnosis to the date of death or the last follow-up visit. Log-rank tests were used to compare survival curves. All statistical analyses used a significance level of 0.05, and all statistical tests were two-sided.

5. Ethical statement

This study was reviewed and approved by the Institutional Review Board of Beijing Tiantan Hospital (grant number: KY 2018-064-02). Informed written consent from patients was waived by the Institutional Review Board of Beijing Tiantan Hospital due to the retrospective study design.

Results

1. Patient characteristics

Among 49 patients included in our study, 34 were males (69.4%). The median age was 13 years (range, 5 to 47 years). Thirty-four patients had their lesions located in the S/SS and PG regions, while 15 patients had their lesions located in the S/SS and BG/T regions. Diagnosis was established based on histology in 13 patients and on levels of serum tumor markers in 36 patients. The non-metastatic status was determined based on both spinal MRI and CSF cytology in 46 patients. The remaining three patients showed negative findings on spinal MRI but had no CSF cytology data due to potential high intracranial pressure. In terms of radiotherapy, three patients underwent FR, 34 patients underwent WBRT plus boost, and 12 underwent CSI plus boost. The total radiation dose was 3,960 cGy in 43 patients, 4,500 cGy in two patients, and 5,040 in four patients. All but two patients in the CSI group received chemotherapy (Table 1).

The most common symptom was adipsic diabetes insipidus, which was documented in 44 patients (89.7%). Visual

Table 1. Patient characteristics

Characteristic	Our cohort (n=49)	Literature cohort (n=81)
Age, median (range, yr)	13 (5-47)	14 (4-28)
Not available	0	41
Primary tumor location		
S/SS+PG	34 (69.4)	81 (100)
S/SS+BG/T	15 (30.6)	0
Sex		
Male	34 (69.4)	27 (33.3)
Female	15 (30.6)	13 (16.0)
Not available	0	41 (50.7)
Method used to make the diagnosis		
Histology	13 (26.5)	64 (79.0)
TM	36 (73.5)	5 (6.2)
Serum β-HCG (IU/L)	14.56 (0.01-74)	-
CSF β-HCG (IU/L)	11.4 (0.01-87.7)	-
Clinical	0	11 (13.6)
Not available	0	1 (1.2)
Radiotherapy		
FR	3 (6.1)	45 (55.6)
WVI	0	17 (20.9)
WBRT+boost	34 (69.4)	4 (4.9)
CSI+boost	12 (24.5)	15 (18.6)
Dose of radiotherapy (Gy)		
≤ 40	43 (87.7)	56 (69.2)
> 40	6 (12.3)	21 (25.9)
Not available	0	4 (4.9)
Patients treated with chemotherapy	47 (95.9)	55 (67.9)

Values are presented as number (%) unless otherwise indicated. S/SS, sellar/suprasellar; PG, pineal gland; BG/T, basal ganglia/thalamus; TM, tumor marker; β-HCG, β-human chorionic gonadotropin; CSF, cerebrospinal fluid; FR, focal radiotherapy; WVI, whole ventricular irradiation; WBRT, whole-brain radiotherapy; CSI, craniospinal irradiation.

acuity decline was reported by 20 patients (40.8%). Sixteen patients (32.7%) had symptoms related to high intracranial pressure. Physical development abnormality was documented in 17 patients, seven of whom had precocious puberty (all male) and 10 had growth retardation (6 male and 4 female). Among 15 patients with S/SS+BG/T germinoma, five presented with hemiparesis.

2. Survival

The median follow-up period was 52 months (range, 10 to 134 months). The estimated 5-year DFS and OS were 96.7% and 97.3%, respectively. During the follow-up, all patients that underwent FR showed disease relapse. Among them, two patients with S/SS+PG germinoma had relapse in the spine and one patient with S/SS+BG/T germinoma had relapse in the left posterior limb of internal capsule. Only one patient with S/SS+PG germinoma in the WBRT group experienced disease relapse (in the spine); all patients in the CSI group were disease-free at the last follow-up. Survival analysis revealed that patients undergoing FR had the low-

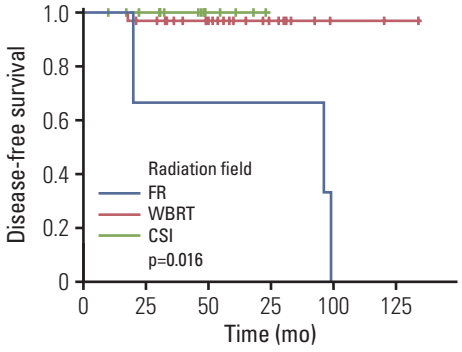

Fig. 2. Comparison of disease-free survival between patients undergoing focal radiotherapy (FR), whole-brain radiotherapy (WBRT), and craniospinal irradiation (CSI) (our cohort). Patients treated with CSI (n=12) or WBRT (n=34) had comparable disease-free survival (p=0.54), but better disease-free survival than those treated with FR (n=3, p=0.016).

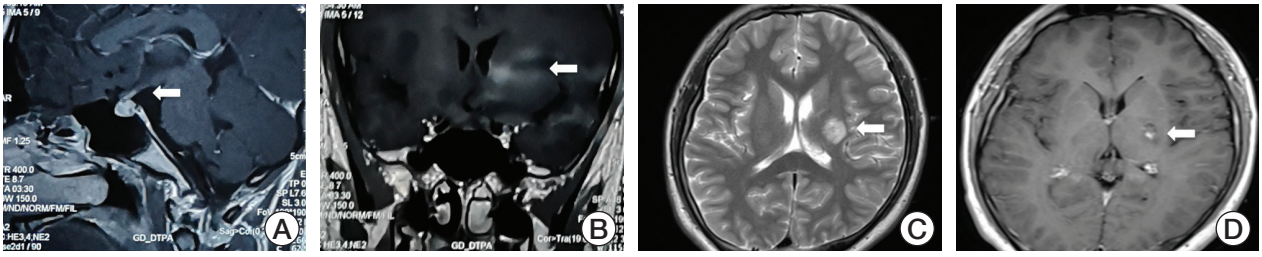

Fig. 3. Images of a 19-year-old boy who presented with adipsic diabetes insipitus only. β-Human chorionic gonadotropin (β-HCG) in the serum and cerebrospinal fluid was 22.4 IU/L and 41.9 IU/L, respectively. (A, B) Radiological examinations revealed pituitary stalk enhancement and left thalamus lesion with enhancement (tumors were indicated by the arrows). Then, four cycles of chemotherapy and focal radiotherapy were applied. (C, D) Twenty months later, enhanced lesion with cyst was identified in the left thalamus area (within the initial radiation field) (tumors were indicated by the arrows). β-HCG in the serum and cerebrospinal fluid was 716 IU/L and 442 IU/L, respectively. Then, salvage chemoradiotherapy was applied.

est DFS (66.6%) (FR vs. WBRT, p=0.008; FR vs. CSI, p=0.046; compared together, p=0.016), while those undergoing either WBRT (96.9%) or CSI (100%) had similar DFS (p=0.540) (Fig. 2).

At the time of relapse, three patients had negative serum/CSF β-HCG and serum β-HCG was 716 IU/L in the fourth patient (Fig. 3). Subsequently, four cycles of chemotherapy and CSI were applied. All patients have been successfully rescued and were disease-free at the last follow-up. The only death in the current cohort was documented in a male patient with histology-proven diagnosis, who underwent WBRT initially. Six years after treatment, left basal ganglia lesion was identified and biopsied. Histology indicated high-grade glioma. He died 2 months later. Consequently, the five-year OS was 100%, 90.9%, and 100% in FR, WBRT, and CSI groups, respectively (p=0.834).

3. Literature cohort

Totally, 81 non-metastatic bifocal germinoma patients were identified from the literature based on the authors' definition [9,12-22]. However, only 51 patients could be confirmed as both spinal MRI negative and CSF cytology negative. All patients had tumors in S/SS and PG regions. In terms of diagnosis, 64 patients were histology-proven, five showed elevated tumor markers, 11 were diagnosed clinically, and one had no available information. Relapses were documented in four of 45 receiving FR, two of 17 receiving whole-ventricle irradiation, 0 of 4 receiving WBRT, and 1 of 15 receiving CSI. DFS was not significantly different between radiation fields (p=0.785) (Fig. 4).

Out of seven relapsed patients, four had spinal lesions. All but one patient received subsequent salvage therapy, including chemoradiotherapy in five and chemotherapy alone in one patient. All were alive at the last follow-up (S2 Table).

4. HRQOL

Out of 48 surviving patients, 46 responded to our survey

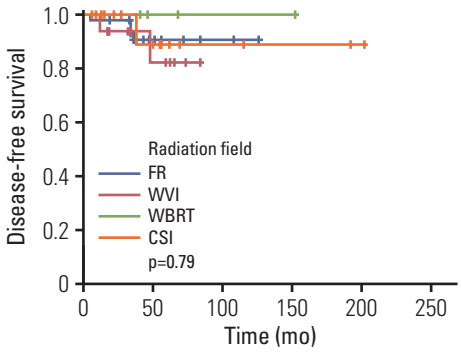

Fig. 4. Comparison of disease-free survival between patients undergoing focal radiotherapy (FR), whole-ventricle irradiation (WVI), whole-brain radiotherapy (WBRT), and craniospinal irradiation (CSI) (literature cohort). Survival analysis did not reveal disease-free survival differences between the types of radiation field (p=0.79).

with 44 having valid paired surveys. Subgroup analysis did not find HRQOL differences between sexes, radiation fields and dose. However, patients with S/SS+BG/T germinoma showed generally lower scores than those with S/SS+PG germinoma. Furthermore, their proxy-report total (p=0.001), emotional score (p=0.020), social score (p=0.018), school score (p=0.001) as well as self-report social score (p=0.024), and school score (p=0.012) were significantly reduced. Besides, better HRQOL were proved in patients surviving > 5 years compared with those surviving ≤ 5 years (Table 2).

Discussion

During the last decades, treatment strategies for patients with intracranial germinoma have greatly improved. Given the excellent prognosis, the primary goal should be to balance the cure rate against long-term toxicity. Thus, minimiz-

Table 2. PedsQL scores and subgroup analyses

	Total	p-value	Physical health	p-value	Emotional	p-value	Social	p-value	School	p-value
Proxy-report										
Sex										
Male (n=31)	71.5±17.7	0.592	69.2±26.2	0.911	78.3±18.88	0.331	75.0±22.5	0.902	65.0±23.6	0.242
Female (n=13)	66.9±19.7		70.7±31.4		70.0±17.7		73.7±19.5		51.2±26.8	
Origin										
S/SS+PG (n=30)	75.4±17.1	0.001	73.1±29.8	0.372	80.3±16.4	0.020	80.6±19.7	0.018	69.0±19.3	0.001
S/SS+BG/T (n=14)	52.6±7.1		60.0±18.6		59.0±15.5		56.0±11.9		31.0±18.8	
Radiation										
Non-CSI[a] (n=34)	79.2±15.2	0.264	81.2±16.3	0.374	81.2±22.5	0.464	82.5±17.0	0.401	70.0±21.2	0.091
CSI (n=10)	67.3±18.5		66.9±29.5		73.4±17.7		72.5±21.7		56.8±26.0	
Dose (Gy)										
≤ 40 (n=40)	66.5±13.1	0.251	68.7±22.8	0.280	74.6±16.1	0.801	70.0±18.5	0.383	51.3±23.1	0.101
> 40 (n=4)	73.1±18.9		77.1±21.7		73.1±17.8		76.3±22.3		63.6±20.4	
Follow-up (yr)										
≤ 5 (n=25)	59.4±13.4	0.007	63.9±19.1	0.403	64.0±15.3	0.002	63.1±16.3	0.013	44.3±16.7	0.001
> 5 (n=19)	76.8±17.2		72.3±31.8		84.1±14.7		82.5±20.1		70.8±20.9	
Self-report										
Sex										
Male (n=31)	65.0±17.1	0.982	65.9±24.5	0.833	68.5±20.4	0.571	68.5±22.8	0.962	56.5±25.8	0.430
Female (n=13)	64.7±24.9		62.5±36.1		62.0±20.7		69.0±24.5		67.0±18.2	
Origin										
S/SS+PG (n=30)	67.3±19.1	0.081	67.5±28.3	0.073	66.5±21.2	0.921	71.5±22.1	0.024	63.8±21.9	0.012
S/SS+BG/T (n=14)	48.9±12.2		46.8±17.6		65.0±14.1		50.0±21.2		35.0±21.2	
Radiation										
Non-CSI[a] (n=34)	79.3±19.5	0.153	84.3±14.3	0.102	80.0±26.4	0.190	81.6±23.6	0.282	68.3±23.6	0.513
CSI (n=10)	71.3±18.09		59.9±28.37		62.9±18.3		65.4±22.1		57.9±23.9	
Dose (Gy)										
≤ 40 (n=40)	65.2±16.9	0.481	67.3±24.5	0.572	67.7±20.1	0.762	67.2±20.4	0.381	57.2±24.6	0.701
> 40 (n=4)	69.4±14.3		72.0±19.1		70.0±18.1		74.0±18.9		60.3±16.7	
Follow-up (yr)										
≤ 5 (n=25)	58.7±14.3	0.141	60.4±18.2	0.474	60.0±16.0	0.143	64.5±19.3	0.364	49.1±17.2	0.042
> 5 (n=19)	69.8±19.5		68.1±31.0		72.0±20.5		73.0±23.2		67.5±22.2	

Values are presented as mean±standard deviation. S/SS, sellar/suprasellar; PG, pineal gland; BG/T, basal ganglia/thalamus; CSI, craniospinal irradiation. [a]Non-CSI group included two patients undergoing FR and 32 patients undergoing whole-brain radiotherapy.

ing the radiation field and dose is a priority, especially for localized disease. Physicians that treat patients with non-metastatic bifocal germinoma face a similar situation, which is challenging for their decision-making. In United States, bifocal germinoma used to be considered as a metastatic disease, and CSI was applied; however, in Europe, it was considered as a localized disease, and FR was applied [8,9,23]. Although emerging evidence shows that limited-field radiation is feasible in this setting, no data are available on the comparison of the efficacy between different radiation fields owing to the rarity of the disease [14,22].

Due to the development of various radiation strategies in our institute, we have an opportunity to compare the efficacy between different radiation fields. As it was shown in our cohort, CSI and WBRT showed comparable DFS, but better DFS than FR. Because WVI is another commonly used limited-field radiation that was not applied in our cohort, we intended to expand our findings based on the literature [9,12-22]. Among 81 patients identified from the literature, there were 7 relapses, including 4/45 receiving FR, 2/17 receiving WVI, 0/4 receiving WBRT, and 1/15 receiving CSI. Survival analysis in the literature cohort did not reveal any differences between CSI and other types of limited-field radiation. Taken together with the findings from our cohort, it could be advocated that limited-field radiotherapy, such as WVI or WBRT, may be considered as an option for patients with non-metastatic bifocal germinoma. We noticed that, among patients undergoing FR, higher relapse rate was observed in our cohort compared with that from the literature. We attributed it to inadequate margins. In some reports with available information, PTV was defined as 2 cm around primary lesions, where the most ventricular area could be covered due to bifocal origins. However, in our cohort, the minimum margins of the three patients that underwent FR were 1.2 cm, 1.3 cm, and 1.6 cm, which may have increased the possibility of tumor cell seeding. But for patient with higher β-HCG level at relapse, possible non-germinomatous germ cell tumors (NGGCTs) components existing could be responsible.

It is still uncertain whether bifocal lesions that presented synchronously at the time of diagnosis arise simultaneously or metastasize from one to the other. All lesions reported from literatures regarding bifocal cases were located in the S/SS and PG regions. Anatomically, both regions are in close contact with ventricles; therefore, CSF may mediate tumor transfer between these two regions. Furthermore, it is not uncommon that patients with localized S/SS or PG germinoma present with metastatic lesions at these sites at the time of treatment failure. Thus, the rationale of limited-field radiation application could be challenged. Interestingly, we identified a number of bifocal germinoma patients with lesions at S/SS and BG/T regions. Tumors originating from the BG/T region were generally surrounded by brain tissue, which showed no direct correlation with other origins. Thus, bifocal germinoma with S/SS and BG/T involvement probably provides another piece of evidence that bifocal germinoma may arise simultaneously in two regions. Consequently, application of limited-field radiation in patients with bifocal germinoma is justified, especially when no other evidence for metastasis is present.

To date, there are three commonly used limited-radiation fields in this setting, including FR, WVI, and WBRT. Many previous studies have shown that FR could lead to higher risk of relapse [9,11,24]. The relapse pattern showed that patients with S/SS and/or PG germinoma had higher risk of periventricular failure after FR [9,24]. Accordingly, WVI was proposed as potential optimal radiation field. Results from a prospective study showed that, among 23 patients with S/SS or PG germinoma, no one relapsed after WVI after 67 months follow-up [25]. However, in patients with BG/T area involvement, WVI may not be adequate since tumor invades deeply in the brain tissue. Probably due to these concerns, WBRT or CSI were the most commonly attempted radiation fields in published reports [26-28]. In our cohort, all 14 patients with non-metastatic S/SS+BG/T bifocal germinoma receiving WBRT were disease-free during the last visit. Based on our findings, WBRT could be considered as optimal radiation field in this population until new evidence emerges, while WVI should be optimal for patients with non-metastatic S/SS+PG bifocal germinoma.

As it was shown in our cohort, at the time of treatment failure, 3/4 relapses were located in the spinal area. Additionally, out of six patients who relapsed after limited-field radiation in the published data, four had spinal failure. Review of baseline evaluation revealed that CSF cytology and spinal MRI were not available for some patients. In our cohort, one patient with spinal failure did not receive CSF examination at diagnosis due to higher intracranial pressure. Therefore, full evaluation of spinal status seems more important in patients with bifocal germinoma, especially when limited-field radiation was considered. Furthermore, we also noticed that, some patients from the literature cohort were diagnosed clinically. A few physicians empirically treated patients with typical bifocal radiological presentations and negative tumor markers as germinoma patients. However, although rare, α-fetoprotein–negative NGGCTs do exist. Since the treatment strategy is totally different between germinoma and NGGCTs, empirical treatment would be problematic. Thus, histology is strongly recommended, especially in patients with negative tumor markers.

Since the onset of germinoma occurs near puberty, HRQOL is always a concern in long-term survivors. Data from our series showed that the HRQOL of patients surviving > 5 years was better. Another study conducted in brain tumor patients receiving proton therapy showed similar results, which HRQOL improving was documented during follow-

up [29]. Besides, we also found that patients with BG/T involvement had lower scores, especially in social and school domains. This finding was also indicated in other studies, which found that patients with BG/T germ cell tumors had worse HRQOL compared with patients with S/SS or PG germ cell tumors. In terms of treatment, some reports indicated that CSI led to lower PedsQL score and more severe neurocognitive impairments compared with limited-field radiations such as FR or WVI [29,30]. Unfortunately, this difference was not validated in our cohort, which may be attributed to WBRT application. However, given that the more extended treatment volume correlates with the higher probability of late-effects that patients encounter, the application of CSI should be confined where possible.

All in all, in the current study, we compared CSI and other limited-field radiation types in patients with non-metastatic bifocal germinoma. Based on the data both from our institute and published literature, CSI showed no advantage in terms of disease control and survival compared with WVI or WBRT. Thus, it is conceivable that CSI may be replaced by limited-field radiation. Furthermore, the HRQOL of this cohort is generally poor, especially for patients with BG/T involvement.

However, limitations do exist. Limited number of cases is still the main obstacle before the convincible conclusions. Although we recruited data from the literature, the inconsistence of screening, diagnosis, and treatments among authors should be concerned. Thus, multicenter study with unified regimen is warranted for the future investigation.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Conflicts of Interest

Conflicts of interest relevant to this article was not reported.

Acknowledgments

This work received financial support from the Beijing Municipal Bureau of Health.

Author Details

[1]Department of Radiation Oncology, Beijing Tiantan Hospital, Capital Medical University, Beijing, [2]Beijing Neurosurgical Institute, Capital Medical University, Beijing, [3]Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, [4]Department of Clinical Nutrition, Beijing Children's Hospital, Capital Medical University, Beijing, [5]Centre of Endocrinology Genetics and Metabolism, National Centre for Children's Health, Beijing Children's Hospital, Capital Medical University, Beijing, China

References

1. Lee SH, Jung KW, Ha J, Oh CM, Kim H, Park HJ, et al. Nationwide population-based incidence and survival rates of malignant central nervous system germ cell tumors in Korea, 2005-2012. Cancer Res Treat. 2017;49:494-501.
2. Murray MJ, Horan G, Lowis S, Nicholson JC. Highlights from the Third International Central Nervous System Germ Cell Tumour Symposium: laying the foundations for future consensus. Ecancermedicalscience. 2013;7:333.
3. Gao Y, Jiang J, Liu Q. Clinicopathological and immunohistochemical features of primary central nervous system germ cell tumors: a 24-years experience. Int J Clin Exp Pathol. 2014;7:6965-72.
4. Wong TT, Chen YW, Guo WY, Chang KP, Ho DM, Yen SH. Germinoma involving the basal ganglia in children. Childs Nerv Syst. 2008;24:71-8.
5. Rasalkar DD, Chu WC, Cheng FW, Paunipagar BK, Shing MK, Li CK. Atypical location of germinoma in basal ganglia in adolescents: radiological features and treatment outcomes. Br J Radiol. 2010;83:261-7.
6. Bamberg M, Kortmann RD, Calaminus G, Becker G, Meisner C, Harms D, et al. Radiation therapy for intracranial germinoma: results of the German cooperative prospective trials MAKEI 83/86/89. J Clin Oncol. 1999;17:2585-92.
7. Maity A, Shu HK, Janss A, Belasco JB, Rorke L, Phillips PC, et al. Craniospinal radiation in the treatment of biopsy-proven intracranial germinomas: twenty-five years' experience in a single center. Int J Radiat Oncol Biol Phys. 2004;58:1165-70.
8. Calaminus G, Frappaz D, Kortmann RD, Krefeld B, Saran F, Pietsch T, et al. Outcome of patients with intracranial non-germinomatous germ cell tumors-lessons from the SIOP-CNS-GCT-96 trial. Neuro Oncol. 2017;19:1661-72.
9. Calaminus G, Kortmann R, Worch J, Nicholson JC, Alapetite C, Garre ML, et al. 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 Oncol. 2013;15:788-96.
10. Goldman S, Bouffet E, Fisher PG, Allen JC, Robertson PL, Chuba PJ, et al. Phase II trial assessing the ability of neoadjuvant chemotherapy with or without second-look surgery to eliminate measurable disease for nongerminomatous germ cell tumors: a children's oncology group study. J Clin Oncol. 2015;33:2464-71.
11. Aoyama H, Shirato H, Ikeda J, Fujieda K, Miyasaka K, Sawamura Y. Induction chemotherapy followed by low-dose involved-field radiotherapy for intracranial germ cell tumors. J Clin Oncol. 2002;20:857-65.
12. Al-Mahfoudh R, Zakaria R, Irvine E, Pizer B, Mallucci CL. The management of bifocal intracranial germinoma in children. Childs Nerv Syst. 2014;30:625-30.
13. Lafay-Cousin L, Millar BA, Mabbott D, Spiegler B, Drake J,

Bartels U, et al. Limited-field radiation for bifocal germinoma. Int J Radiat Oncol Biol Phys. 2006;65:486-92.
14. Huang PI, Chen YW, Wong TT, Lee YY, Chang KP, Guo WY, et al. Extended focal radiotherapy of 30 Gy alone for intracranial synchronous bifocal germinoma: a single institute experience. Childs Nerv Syst. 2008;24:1315-21.
15. Weksberg DC, Shibamoto Y, Paulino AC. Bifocal intracranial germinoma: a retrospective analysis of treatment outcomes in 20 patients and review of the literature. Int J Radiat Oncol Biol Phys. 2012;82:1341-51.
16. van Battum P, Huijberts MS, Heijckmann AC, Wilmink JT, Nieuwenhuijzen Kruseman AC. Intracranial multiple midline germinomas: is histological verification crucial for therapy? Neth J Med. 2007;65:386-9.
17. Merchant TE, Sherwood SH, Mulhern RK, Rose SR, Thompson SJ, Sanford RA, et al. CNS germinoma: disease control and long-term functional outcome for 12 children treated with craniospinal irradiation. Int J Radiat Oncol Biol Phys. 2000;46:1171-6.
18. Ogawa K, Yoshii Y, Shikama N, Nakamura K, Uno T, Onishi H, et al. Spinal recurrence from intracranial germinoma: risk factors and treatment outcome for spinal recurrence. Int J Radiat Oncol Biol Phys. 2008;72:1347-54.
19. Baranzelli MC, Patte C, Bouffet E, Couanet D, Habrand JL, Portas M, et al. Nonmetastatic intracranial germinoma: the experience of the French Society of Pediatric Oncology. Cancer. 1997;80:1792-7.
20. Cuccia V, Alderete D. Suprasellar/pineal bifocal germ cell tumors. Childs Nerv Syst. 2010;26:1043-9.
21. Shikama N, Ogawa K, Tanaka S, Toita T, Nakamura K, Uno T, et al. Lack of benefit of spinal irradiation in the primary treatment of intracranial germinoma: a multiinstitutional, retrospective review of 180 patients. Cancer. 2005;104:126-34.
22. Sugiyama K, Uozumi T, Arita K, Kiya K, Kurisu K, Sumida M, et al. Clinical evaluation of 33 patients with histologically verified germinoma. Surg Neurol. 1994;42:200-10.
23. Rogers SJ, Mosleh-Shirazi MA, Saran FH. Radiotherapy of localised intracranial germinoma: time to sever historical ties? Lancet Oncol. 2005;6:509-19.
24. Alapetite C, Brisse H, Patte C, Raquin MA, Gaboriaud G, Carrie C, et al. Pattern of relapse and outcome of non-metastatic germinoma patients treated with chemotherapy and limited field radiation: the SFOP experience. Neuro Oncol. 2010;12:1318-25.
25. Lee DS, Lim DH, Kim IH, Kim JY, Han JW, Yoo KH, et al. Upfront chemotherapy followed by response adaptive radiotherapy for intracranial germinoma: prospective multicenter cohort study. Radiother Oncol. 2019;138:180-6.
26. Bowzyk Al-Naeeb A, Murray M, Horan G, Harris F, Kortmann RD, Nicholson J, et al. Current management of intracranial germ cell tumours. Clin Oncol (R Coll Radiol). 2018;30:204-14.
27. Sonoda Y, Kumabe T, Sugiyama S, Kanamori M, Yamashita Y, Saito R, et al. Germ cell tumors in the basal ganglia: problems of early diagnosis and treatment. J Neurosurg Pediatr. 2008;2:118-24.
28. Kamoshima Y, Sawamura Y. Update on current standard treatments in central nervous system germ cell tumors. Curr Opin Neurol. 2010;23:571-5.
29. Kuhlthau KA, Pulsifer MB, Yeap BY, Rivera Morales D, Delahaye J, Hill KS, et al. Prospective study of health-related quality of life for children with brain tumors treated with proton radiotherapy. J Clin Oncol. 2012;30:2079-86.
30. Liang SY, Yang TF, Chen YW, Liang ML, Chen HH, Chang KP, et al. Neuropsychological functions and quality of life in survived patients with intracranial germ cell tumors after treatment. Neuro Oncol. 2013;15:1543-51.