Journal of Radiation Research, Vol. 64, No. 2, 2023, pp. 428–437
https://doi.org/10.1093/jrr/rrac095
Advance Access Publication: 5 January 2023

Salvage craniospinal irradiation for recurrent intracranial germinoma: a single institution analysis

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(Received 17 July 2022; revised 12 September 2022; editorial decision 21 November 2022)

ABSTRACT

This study investigated the effectiveness and safety of low-dose salvage craniospinal irradiation (CSI) for recurrent germinoma. We retrospectively reviewed long-term tumor control and late adverse effects in 15 recurrent germinoma patients treated at our hospital between 1983 and 2019. Following the first recurrence of germinoma, seven were treated with 24–30 Gy of salvage CSI, three underwent non-CSI, and five were treated with only chemotherapy. CSI achieved a significantly better recurrence-free survival rate after the first recurrence compared to other strategies (100% vs 33%, $p < 0.001$: log-rank test). To evaluate the safety of salvage CSI, we assessed the outcomes at the final follow-up of seven patients who received salvage CSI at first recurrence and three patients who received salvage CSI at second recurrence. The median follow-up period was 220 months after initial treatment. Five patients who received 40–50 Gy of radiation therapy or underwent multiple radiation therapy before salvage CSI were classified into Group A, whereas five patients treated with platinum-based chemotherapy and 24–32 Gy of radiation therapy to the primary site, whole ventricle, or whole brain were classified into Group B. In Group A, one had endocrine dysfunction and the other had visual dysfunction. None were socially independent. Meanwhile, in Group B, no endocrine or visual dysfunction was found, and three patients were socially independent. Salvage CSI achieved excellent tumor control in recurrent germinoma and was safe in patients initially treated with low-dose radiation therapy and chemotherapy.

Keywords: recurrent intracranial germinoma; radiation therapy; salvage therapy; long-term results

INTRODUCTION

Intracranial germinoma commonly affects adolescents and young adults. Its standard treatment has been identified to be radiation therapy or chemotherapy, followed by reduced-dose radiation to the ventricle. This treatment produces 10-year overall survival rates of > 90% [1, 2]. However, some patients suffer repeated recurrence after insufficient initial and salvage treatments [2–5]. Various salvage treatments for germinoma have been reported, including craniospinal irradiation (CSI), standard chemotherapy and reduced-dose radiation therapy, and high-dose chemotherapy with autologous stem cell rescue [3, 5–13]. Although recurrent germinoma responds to these salvage treatments in the short term, no standard treatment has been established because there is insufficient information on the long-term tumor control and complications of salvage treatments [14].

Salvage CSI has been identified as one of the most effective strategies for recurrent germinoma [9] as irradiation not covering the craniospinal axis often results in further recurrence outside the previous radiation field [15]. However, CSI can cause long-term complications, including endocrine dysfunctions, short stature, neurocognitive dysfunctions, secondary neoplasms, radiation necrosis

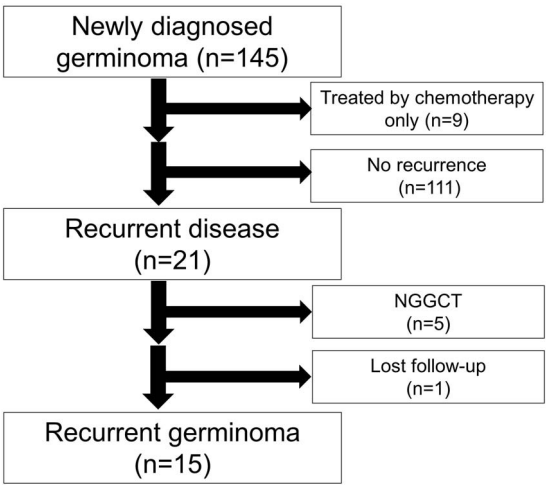

Fig. 1. Inclusion and exclusion criteria for germinoma patients in this study.

and cerebrovascular diseases [16–23]. These complications can be frequent and severe in young children with medulloblastoma, ependymoma and acute lymphoblastic leukemia [16–23], but their frequency and severity in patients with germinoma have not yet been established.

In this study, we retrospectively analyzed the long-term complications and ongoing tumor control capacity of salvage CSI for recurrent germinoma to determine the efficacy and safety of salvage CSI for recurrent germinoma.

MATERIALS AND METHODS

Patient characteristics

We conducted a retrospective review of the medical records of our department and identified 145 patients treated for newly diagnosed intracranial germinoma between January 1983 and December 2019. Nine patients were treated with only chemotherapy, and were excluded from this study. Only chemotherapy is currently not indicated for patients with newly diagnosed germinoma due to its high recurrence rate [2]. During the study period, 21 of the remaining 136 patients suffered recurrence; of these 21 cases, four had histologically verified non-germinomatous germ cell tumors (NGGCTs) [24] and 1 had clinically diagnosed NGGCT with significant elevation of α-fetoprotein (AFP) levels. These patients received intensive treatment and were excluded from our sample (Fig. 1 and Supplementary Table S1).

Treatments

Newly diagnosed germinomas were treated with irradiation to the focal field, the whole affected ventricle, the whole brain, or the craniospinal axis, with or without chemotherapy [17]. This protocol was noted to vary during the study period. In brief, the treatment protocol between 1983 and 1995 consisted of radiation therapy of 40–60 Gy to the primary site, with or without chemotherapy [2, 25–27]. From 1995, three regimens of platinum-based chemotherapy were introduced for the treatment of germinoma. These were CARE, comprising three cycles of chemotherapy with a combination of carboplatin (150 mg/m^2) and etoposide (150 mg/m^2) on days 1–3; PE, comprising three cycles of a combination of cisplatin (20 mg/m^2) and etoposide (60 mg/m^2) once a day for 5 consecutive days; and ICE, comprising three cycles of a combination of ifosfamide (900 mg/m^2), cisplatin (20 mg/m^2) and etoposide (60 mg/m) once a day for 5 consecutive days. Between 1995 and 1996, patients were treated with only chemotherapy. The treatment protocol in 1997 was CARE or ICE chemotherapy, followed by reduced-dose radiation therapy to the local site. After 1998, the protocol was CARE or ICE chemotherapy, followed by reduced-dose radiation therapy to the larger field covering at least the whole ventricle. The radiation field was modified according to the distribution of the tumor. Patients with positive cerebrospinal fluid (CSF) cytology and/or spinal dissemination on magnetic resonance imaging (MRI) received 24 Gy of radiation therapy to the craniospinal axis [28], whereas patients with basal ganglia germinoma received 24 Gy to the whole brain.

Until August 2006, recurrent germinomas were treated with chemotherapy only or with chemotherapy and salvage radiation therapy covering the local recurrence site or whole brain to avoid the late complications caused by salvage CSI (Table 1). The chemotherapy regimen was PE, ICE and BEP comprising three cycles of a combination of bleomycin (20 mg/m^2) on days 1, 7 and 14, etoposide (60 mg/m^2) on days 1–5 and cisplatin (20 mg/m^2) on days 1–5. After 2006, all patients with recurrent germinoma received ICE chemotherapy, followed by 24 Gy (2 Gy per fraction once a day) (n = 8) or 30 Gy (1.2 Gy per fraction twice a day) of reduced-dose salvage CSI, irrespective of prior radiation therapy, to achieve tumor control.

Typical radiation therapy at our institution uses either a 2- or 3D technique. The treatment is delivered using a 10-megavoltage photon beam linear accelerator equipped with a multileaf collimator. A daily dose of 2 Gy for 5 consecutive days a week is administered. Whole ventricle irradiation and whole brain irradiation are performed using lateral-opposed fields with the patient in the supine position wearing a thermoplastic immobilization mask. CSI is performed with the patient in the supine or prone position wearing a thermoplastic immobilization mask. A three-isocenter approach is then used, consisting of lateral-opposed fields to the whole brain and a single posterior field to the upper and lower portions of the spine. A 5 mm gap is left between radiation fields to avoid overdose to at-risk organs. Using two patterns of radiation planning, the position of the gap is shifted every other day.

FOLLOW-UP AND ESTIMATION OF LONG-TERM OUTCOMES

In the 3 years after initial treatment, patients are followed up with MRI every 3 months. This is then reduced to every 4 months until 5 years after initial treatment, then every 6 months until 10 years, and once a year thereafter.

Endocrine function is estimated from serum levels of luteinizing hormone, follicle-stimulating hormone, testosterone, progesterone, insulin-like growth factor-2, thyroid-stimulating hormone, free triiodothyronine, free thyroxine, adrenal corticotropic hormone and cortisol. Visual function is estimated using tests of visual acuity and assessment of the visual field. Employment status classifications were as follows: job in a normal workspace, student, job in a sheltered

Table 1. Demographics of germinoma patients with recurrence

Case number	Age	Sex	Primary lesion						First recurrence							Second recurrence				Overall survival after initial treatments (months)
			Tumor location	Histological diagnosis	Tumor marker (Serum/ CSF)		Initial treatment		Interval from initial treatment to first recurrence (months)	Site of recurrece	Histological diagnosis	Tumor marker (Serum/ CSF)		Salvage treatments		Interval from first and second recurrence (months)	Site of second recurrence	Salvage treatments at second recurrence		
					HCG (mIU/ml)	HCG-β (ng/ml)	Chemotherapy	Radiation				HCG (mIU/ml)	HCG-β (ng/ml)	Chemotherapy	Radiation			Chemotherapy	Radiation	
1	9	M	B	N.E.	1.5/ N.A.	0.77/ N.A.	N	LBI 49Gy	52	V	N.E.	N.A./ N.A.	<0.1/ N.A.	BEPx3	None					355
2	11	M	N	Pure germinoma	<1.0/ 1.4	0.33/ 1.5	N	LBI 50Gy	9	V	N.E.	N.A./ N.A.	0.11/ N.A.	BEPx1	None					219 [a]
3	11	M	B	N.E.	10.5/ 45.2	0.29/ 1.15	N	LBI 50Gy	56	V	Positive cytology	N.A./ N.A.	0.12./ 0.17	PEx3	None	13	V	ICE x3	None	248
4	15	M	P	N.E.	N.A./ N.A.	2.71/ 2.97	N	LBI 30Gy WBI 20Gy	47	Sp	Pure germinoma	N.A./ N.A.	0.31/N.A.	PEx3	WSI 24Gy					301
5	21	M	P	N.E.	0.2/ N.A.	N.A./N.A.	N	LBI 48.6Gy	22	Pr	Pure germinoma	N.A./ N.A.	<0.1/N.A.	PEx3	LBI 24Gy					319
6	45	M	B	N.E.	2.2/ 2.5	0.32/ 0.05	N	LBI 50Gy	37	Sp	Pure germinoma	N.A./ N.A.	1.5/ 0.29	PEx2	None	55	Pr	None	LBI20Gy, CSI 24Gy	204 [b]
7	8	M	N	N.E.	28/ N.A.	0.2/ 0.49	N	LBI 55.6Gy	152	V	N.E.	<1.0/ 2.9	<0.1/0.36	ICEx3	None	4	V	ICEx3	CSI 30Gy*	323
8	7	M	P	N.E.	0.4/ N.A.	N.A./ 1.9	N	WVI 24Gy, SRS 12 Gy	19	CPA, Sp	N.E.	N.A./ N.A.	<0.1/N.A.	ICEx3	CSI 30Gy					224
9	14	M	BG	Pure germinoma	N.A./N.A.	N.A./N.A.	N	LBI 20Gy* WBI 30Gy*	216	Sp, Op	N.E.	1.3/ 14.1	<0.1/ 0.3	ICEx3	CSI 24Gy					276
10	14	M	B	N.E.	N.A./ <0.6	N.A./N.A.	CAREx 2	LBI 23.4Gy**	44	Op	N.E.	1.9/ 2.1	<0.1/N.A.	ICEx3	WBI 24Gy,	16	Sp	ICEx3	CSI 24Gy	220
11	12	F	N	Pure germinoma	N.A./N.A.	0.54/ 0.39	PE x 3	LBI 24Gy	151	V	N.E.	<1.0/ 6.3	<0.1/ 0.3	ICEx3	CSI 24Gy					290
12	21	M	B	N.E.	N.A./N.A.	2.0/ N.A.	N	LBI 32Gy, LSI 32Gy	26	Op	N.E.	6.8/ 27.8	<0.1/ 0.58	ICEx3	CSI 30Gy*					192
13	10	M	B	N.E.	<1.0/ N.A.	<0.1/ N.A.	CARE X3	WVI 24Gy	31	Op	N.E.	10.9/ N.A.	0.33/ N.A.	ICEx3	CSI 24Gy					123
14	18	M	P	Pure germinoma	16.5/ 60	N.A./N.A.	CARE X3	WVI 24Gy	99	Pr	N.E.	<1.0/ 2.6	<0.1/ 0.2	ICEx3	CSI 24Gy					210
15	8	M	BG	pure germinoma	N.A./N.A.	0.13/ N.A.	ICEx3, CARE5	WBI 24Gy	99	Pr	N.E.	<1.0/ 5.0	<0.1/ 0.3	ICEx3	CSI 24Gy					204

Abbreviations: M = Male; F = female; B = Bifocal; N = Neurohypophyseal; P = Pineal; BG = Basal ganglia; N.E. = Not examined; N.A. = Not analyzed; CSF = Cerebrospinal fluid: HCG = human chorionic gonadotropin; HCG-β = human chorionic gonadotropin- β subunit; IU = international unit; N = None, CARE = Carboplatin and etoposide; PE = Cisplatin and etoposide; ICE = Ifosfamide, cisplatin and etoposide; LBI = Local brain irradiation; WBI = Whole brain irradiation; SRS = Stereotactic radiosurgery; WVI = whole ventricle irradiation; LSI = Local spine irradiation; V = Ventricular wall; Sp = Spinal cord; Pr = Primary site; CPA = Cerebellopontine angle; Op = Optic nerve; BEP = Bleomycin, etoposide and cisplatin; CSI = Craniospinal irradiation; * = Hyperfractionated irradiation (1.2Gy per fraction) ; ** = 1.8 Gy/fraction; a = Died of panhypopituitarism; b = Died of pneumonia

workplace for people with mental or physical disabilities, or not in education, employment, or training and dependent on parents due to physical disability [1]. In patients aged 16 years or over, intelligence was assessed using the Wechsler Adult Intelligence Scale-revised or third edition. For patients aged under 16 years, the Wechsler Intelligence Scale for Children-revised or third edition was used. Microbleeds were assessed using T2*-weighted MRI in accordance with previous literature [29].

STATISTICAL ANALYSIS

The two groups were compared using Student's t-tests for continuous variables and Fisher's exact tests for categorical variables. To analyze the tumor control rate of the salvage therapy, the progression-free survival time after recurrence was defined as months from the date of recurrence diagnosis to that of either further recurrence or the last day of follow-up. The progression-free survival rates were calculated using the Kaplan–Meier method. Statistical analyses were performed using Prism software (GraphPad, San Diego, CA, USA). Statistical significances were calculated using log-rank tests. A p-value of < 0.05 was considered statistically significant.

RESULTS

Initial patient characteristics

A total of 145 patients were treated during the study period, 136 patients received radiation therapy with or without chemotherapy, and nine received only chemotherapy (Fig. 1). The recurrence rate of initial treatment is shown in Supplementary Table S1. As reported previously [2], radiation therapy to the primary site results in a high rate of recurrence. In this study, we analyzed 15 patients with recurrent germinoma excluding one patient lost to follow-up and four patients with recurrent NGGCT (Fig. 1 and Supplementary Table S1). The clinical features of these patients at initial presentation and recurrence are summarized in Table 1. The patients were 14 males and one female, aged 7–45 years (median 12 years) at initial presentation and 9–54 years (median 22 years) at recurrence. At initial presentation, the tumor location was the pineal gland in four cases, the neurohypophysis in three, the basal ganglia in three and a bifocal lesion of the pineal gland and neurohypophysis in six. The diagnosis of germinoma was histological in five patients and clinical in 10. No patient exhibited elevated level of AFP or positive CSF cytology, or elevation of serum or CSF levels of human chorionic gonadotropin (HCG) or HCG-β.

Eight patients were treated with high-dose radiation therapy of 48.6–55.6 Gy (median 50 Gy) to the primary site (Cases 1–7 and 9), whereas one patient (Case 8) was treated with 12 Gy of gamma knife irradiation and 24 Gy of whole ventricle irradiation [30]. Six patients were treated with low-dose radiation (Cases 10–15). Of these, three received 23.4–32 Gy to the local site, two received 24 Gy to the whole ventricle, and one received 24 Gy to the whole brain. This treatment was combined with platinum-based chemotherapy in five of the six patients.

Patient characteristics at recurrence

Figure 2A shows the Kaplan–Meier curves for progression-free survival of recurrent germinoma patients after initial treatment. Recurrence of the disease developed 9–216 months (median, 47 months) after the initial treatment. In six (40%) and three (20%) of the patients, recurrence occurred after more than 5 and 10 years, respectively. A recurrent lesion was found in the ventricular wall in five patients, in the optic nerve or chiasma distant from the neurohypophysis in four, in the spinal cord in four, in the cerebellopontine angle in one, and at the primary site in three. All recurrent lesions, except those at the primary site, were located outside the radiation field. No elevation was seen in serum or CSF AFP levels, and serum or CSF HCG/HCG-β was undetectable in three patients and modestly elevated in 12. Moreover, three patients had received histological diagnoses of recurrent germinoma, one patient had positive CSF cytology compatible with germinoma, and 11 patients were diagnosed based on clinical findings.

Tumor control after salvage treatment

To evaluate the effect of salvage therapy, salvage treatment for the first recurrence was classified into only chemotherapy (only chemotherapy group, n = 5), platinum-based chemotherapy and radiation therapy not covering the whole craniospinal axis (non-CSI group, n = 3), and chemotherapy and reduced-dose radiation therapy to the whole craniospinal axis (CSI group, n = 7) (Fig. 3) [9]. All patients showed complete response or partial response to salvage treatment. In the long-term, salvage CSI achieved a significantly better progression-free survival rate after initial recurrence than the other treatment strategies (100% vs 33%, $p < 0.001$). Early progression was seen in one of the three patients in the non-CSI group and three of the five in the only chemotherapy group (Fig. 2B).

Four patients developed second recurrence. One patient (Case 3) was treated with only chemotherapy. Three patients (Cases 6, 7 and 10) underwent salvage treatments other than CSI at first recurrence (Fig. 3). These three patients then received salvage CSI with or without ICE chemotherapy after second recurrence, and maintained complete remission for 110, 136 and 140 months after the second recurrence (Table 1). These results suggest that reduced-dose salvage CSI can provide excellent tumor control at first and second recurrences compared to other strategies.

Long-term complications after salvage CSI

Long-term complications in the 10 patients who received reduced-dose salvage CSI are shown in Table 2. The median interval from initial treatment to reduced-dose salvage CSI was 98 months; from salvage CSI to last follow-up, 123 months; and from initial treatment to final follow-up, 220 months (Table 2). Nine patients remained alive, and one died of pneumonia following a gradual decline in performance status caused by progressive brain atrophy in the bilateral frontal lobes (Case 6 in Supplementary Fig. 1).

To evaluate the safety of salvage CSI, the dosage and field of irradiation prior to salvage CSI were deemed important. Therefore, patients who received salvage CSI for recurrent germinoma were divided into two groups based on prior radiation therapy (Fig. 3). Group A was consisted of five patients who received high-dose radiation therapy of 40–50 Gy (Case 6, 7 and 9), stereotactic radiosurgery to the primary site (Case 8), or multiple courses of radiation therapy before salvage CSI (Case 10); and Group B of five patients who were treated with

Table 2. Demographic and long-term outcomes of the patients treated with salvage CSI

Case number	Group	Radiation therapy			Age at initial treatment (year-old)	Age at CSI (year-old)	Intervals from initial treatment and CSI (months)	Interval from CSI to last follow-up (months)	Interval from initial treatment to last follow-up (months)	Newly developed endocrine dysfunction after salvage treatment	Newly developed visual dysfunction after salvage treatment	Social status	Decline in FSIQ (> 10 points)	Atropy	Micro-bleeds
		Initial treatment	First recurrnce	Second recurrence											
6	A	LBI 50Gy	None	LBI20Gy, CSI 24Gy	45	54	93	111	204[a]	N	N	dead	N.E.	Y	N.E.
7	A	LBI 50Gy	None	CSI 30Gy*	8	21	157	166	323	N	N	Sheltered workshop	Yes	N	>10
8	A	WVI 24Gy, SRS 12Gy	CSI 30Gy		7	9	19	205	224	T,G	N	Sheltered workshop	No	N	< 10
9	A	LBI 20Gy* WBI 30Gy*	CSI 24Gy		14	32	216	60	276	N	N	Dependent on his parents	N.E.	Y	>10
10	A	LBI 23.4Gy**	WBI 24Gy	CSI 24Gy	14	19	60	160	220	N	progressive	Dependent on his parents	Yes	Y	< 10
11	B	LBI 24Gy	CSI 24Gy		12	24	155	135	290	N	N	House wife/ Part time job	N.E.	N	< 10
12	B	LBI 32Gy, LSI 32Gy	CSI 30Gy*		21	23	19	173	192	N	N	Domestic help	N.E.	N	>10
13	B	WVI 24Gy	CSI 24Gy		10	12	23	100	123	N	N	College student	N.E.	N	< 10
14	B	WVI 24Gy	CSI 24Gy		18	27	104	106	210	N	N	Fulltime job	No	Y	>10
15	B	WBI 24Gy	CSI 24Gy		8	16	102	102	204	N	N	Sheltered workshop	No	Y	>10

Abbreviations: CSI = Craniospinal irradiation; LBI = Local brain irradiation; WVI = whole ventricle irradiation; SRS = Stereotactic radiosurgery; WBI = Whole brain irradiation; LSI = Local spine irradiation; T = Thyroid hormone; G = Growth hormone; Y = Yes; N = No; N.E. = Not examined; WMS-R = Wechsler memory scale- revised edition; * = Hyperfractionated irradiation (1.2Gy per fraction) ; ** = 1.8 Gy/fraction; a = Died of pneumonia,

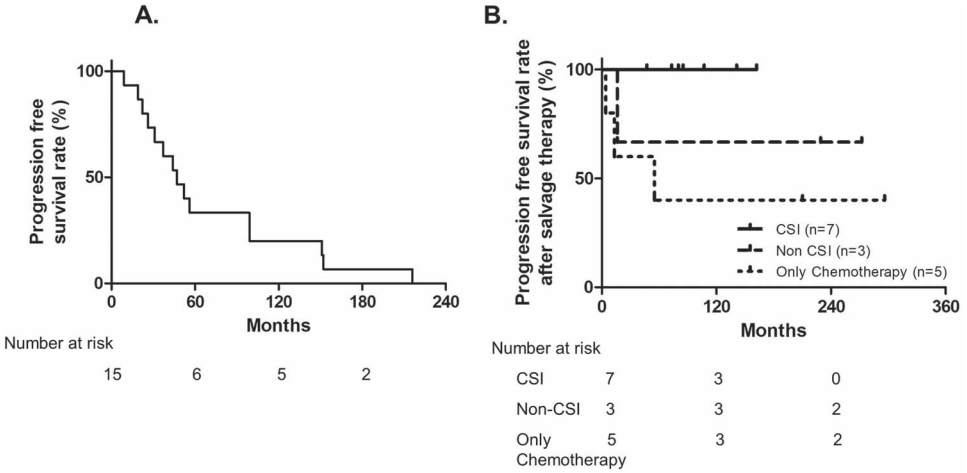

Fig. 2. Kaplan–Meier curves for the progression-free survival rates of patients with recurrent germinoma. Dates are from the start of initial treatment (A) and salvage therapy to recurrent disease (B).

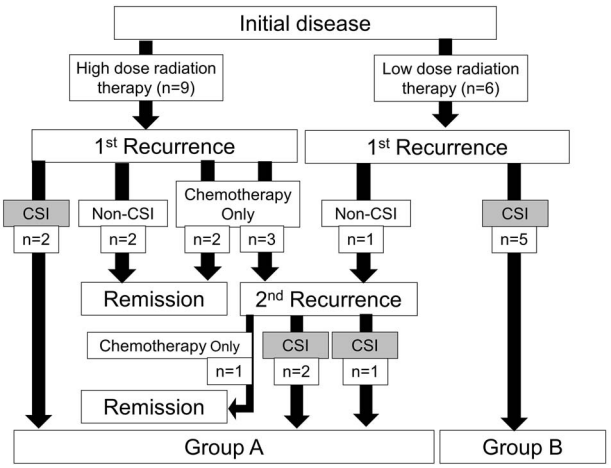

Fig. 3. Treatment for first and second recurrences of germinoma and classification for the estimation of safety of salvage CSI for recurrent germinoma. Patients who received high-dose radiation therapy, including stereotactic radiosurgery, to the primary site, or multiple courses of radiation therapy before salvage CSI were classified as Group A; patients who were treated with platinum-based chemotherapy and low-dose radiation therapy to the primary site, the whole ventricle, or the whole brain were classified as Group B.

platinum-based chemotherapy and low-dose radiation therapy of 24–32 Gy to the primary site, the whole ventricle, or the whole brain (Table 2).

Prior treatments in each group and patient demographics are shown in Tables 2 and 3. Groups A and B exhibited no differences in age at onset, interval from first radiation therapy to reduced-dose salvage CSI, age at reduced-dose salvage CSI, or the interval from initial treatment to final follow-up (Table 3). The median follow-up after CSI was 160 months in Group A and 106 months in Group B.

We then reviewed endocrine function, visual function, employment status, transectional and longitudinal intelligence quotients (IQ) and MRI findings before reduced-dose CSI and at follow-up. Three patients in Group A (Cases 6, 7 and 10) and three patients in Group B (Cases 11–13) had panhypopituitarism at onset. One patient in Group A (Case 8) had newly developed primary hypothyroidism and adult growth hormone deficiency 20 months and 204 months after reduced-dose salvage CSI, respectively. No other patients required additional hormone replacement after reduced-dose salvage CSI.

One patient in Group A (Case 10) had progressive deterioration of visual acuity after reduced-dose salvage CSI and was completely dependent on his parents. In Group B, three patients (Cases 11, 13 and 14) were living independently, and two (Cases 12 and 15) worked at sheltered workshops. In contrast, none of the patients in Group A were independent. Two patients (Cases 7 and 8) worked at sheltered workshops, while two (Cases 9 and 10) required assistance in daily life due to visual and motor dysfunctions.

IQs were evaluated in eight patients and longitudinal IQ in six patients (Fig. 4). All three of the Group B patients with longitudinal IQ estimation showed stable verbal, performance and full-scale IQ. One patient had an IQ score > 100 at 69 months after salvage CSI. In Group A, two of three patients with longitudinal evaluation of IQ had decline in IQ. Case 7 showed a progressive decline in verbal, performance and full-scale IQ after salvage CSI for unknown reasons, whereas Case 10 showed a marked decline in performance IQ due to deterioration of their visual function.

Longitudinal MRI findings after reduced-dose salvage CSI are shown in Supplementary Figs 1 and 2. Follow-up MRI found no radiation necrosis, white matter encephalopathy, secondary neoplasms, or radiation-induced vasculopathy. Progressive cerebral atrophy was found in three patients (Cases 6, 8 and 10) in Group A and one patient (Case 14) in Group B. More than 10 microbleeds altogether were found in two patients (Cases 7 and 9) in Group A and three patients (Cases 12, 14 and 15) in Group B.

Table 3. Clinical characteristics of the patient treated by salvage CSI in Group A and B

	All cases (n=10)	Group A (n=5)	Group B (n=5)	p-value*
Age at initial presentation (years old) (median)	7–45 (13)	7–45 (14)	8–21 (12)	0.62
Age at CSI (year-old) (median)	9–54 (22)	9–54 (21)	12–27 (23)	0.44
Intervals from initial treatment and CSI (months) (median)	19–216 (98)	19–216 (93)	19–155 (102)	0.53
Interval from CSI to last follow-up (months) (median)	60–205 (123)	60–205 (160)	100–173 (106)	0.56
Interval from initial treatment to last follow-up (months) (median)	123–323 (220)	204–323 (224)	129–290 (204)	0.22

Abbreviations: CSI = Craniospinal irradation; * Students' t-test between Group A and B

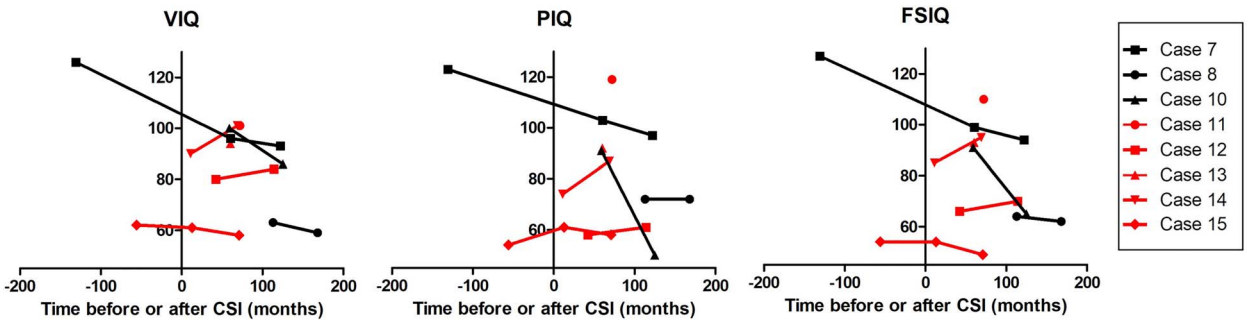

Fig. 4. IQs of recurrent germinoma patients before and after treatment with low-dose salvage CSI. In patients under 16 years, IQ was measured using the Wechsler Intelligence Scale for Children-revised or third edition. Patients over 16 years were tested using the Wechsler Adult Intelligence Scale-revised or third edition. The transverse axis indicates the time before or after salvage CSI. Patients in Groups A and B are indicated in black and red, respectively.

DISCUSSION

The present study evaluated the long-term effects and safety of salvage CSI for recurrent germinoma, with a median follow-up period of 220 months after initial treatment. Reduced-dose salvage CSI was found to be the most effective means of controlling recurrent disease, and a safe treatment for patients initially treated with chemotherapy and reduced-dose radiation therapy to the local site, whole ventricle, or whole brain.

Nowadays, germinoma rarely recurs after improved treatments, such as chemotherapy followed by 24 Gy of radiation therapy covering at least the whole ventricle for newly diagnosed patients. However, recurrence can sometimes develop after long-term follow-up [3]. Consequently, the standard treatment for recurrent germinoma that should follow the current standard treatment for newly diagnosed germinoma is difficult to establish. A few reports have discussed the effect of salvage CSI on recurrent germinoma, but did not evaluate long-term complications [3, 8, 9].

Effects of salvage treatment on recurrent germinoma

Reduced-dose salvage CSI was determined to have excellent and durable tumor control against the first or second recurrence of germinoma with a follow-up period after CSI of 60–205 months (median 123 months). Although recurrence of the disease has been found to respond to both chemotherapy only and with radiation therapy to a limited field in this study, frequent early recurrence was found after these treatments. A previous study demonstrated excellent tumor control after salvage CSI in 14 treated patients and 88 patients retrospectively reviewed from the literature [9]. Another study compared nine patients treated with reduced-dose CSI (18–25.2 Gy, median 24 Gy) with 15 treated with radiation therapy not covering the craniospinal axis. None of the nine CSI patients suffered recurrence, whereas seven of the 15 non-CSI patients died of disease progression [3]. The present findings of the effectiveness of reduced-dose salvage CSI are consistent with these previous reports.

In contrast, the effects of chemotherapy and reduced-dose radiation therapy not covering the craniospinal axis are somewhat mixed. In a study that treated six recurrent germinoma patients with chemotherapy and reduced-dose radiation therapy not covering the entire craniospinal axis, none of the six had second recurrence. In the same study, seven of nine patients treated with focal or whole-brain radiation therapy without chemotherapy suffered tumor progression [3]. In our study, one of three patients (Case 10) treated with chemotherapy and non-CSI suffered early recurrence in the spinal cord, outside the radiation field covered by salvage whole brain irradiation. Therefore, we believe that chemotherapy and non-CSI are insufficient to achieve effective tumor control.

High-dose chemotherapy with peripheral stem cell rescue has been reported to be effective [6, 8, 10, 12], but second recurrences were noted to be frequent when this treatment is not combined with CSI [6, 8]. The addition of CSI to high-dose chemotherapy is associated with better outcomes [7]. Therefore, high-dose chemotherapy with stem cell rescue may be considered effective alongside radiation therapy. However, another study found high-dose chemotherapy effective against recurrent germinoma without radiation therapy, with four of six

patients surviving without recurrence after high-dose chemotherapy without salvage irradiation for 12, 96, 112 and 114 months [27]. The authors speculated that intensive chemotherapy prior to high-dose chemotherapy may result in a more profound complete response of recurrent disease [11].

Safety of reduced-dose salvage CSI

There have been no reports demonstrating the long-term safety of salvage CSI for recurrent germinoma. We present the complications associated with salvage CSI during long-term follow-up (median 123 months). Endocrine function, visual function, intelligence and employment status were relatively well preserved in Group B patients compared to those in Group A.

Irradiation dosages tolerated by the brain and spinal cord have been determined, based on the development of brain tissue necrosis and radiation-induced myelopathy [31–36]. Reirradiation of the brain, or other organs, can be harmful if recovery is insufficient from the first irradiation [32]. Therefore, potential adverse effects can be predicted based on the interval between the first and second irradiation, the cumulative dose, and the maximum dose used for each course [33, 35]. These predictors of adverse responses to reirradiation of the central nervous system have been analyzed in detail in the spinal cord. The risk of radiation myelopathy was determined to be low after a cumulative biologically effective dose (BED) of < 135.5 Gy_2 ($\alpha/\beta = 2$) and a maximum dose for each course of < 98 Gy_2 ($\alpha/\beta = 2$) provided the interval between courses is greater than 6 months [37]. In the present study, the BED was 80 Gy_3 ($\alpha/\beta = 3$) or 96 Gy_2 ($\alpha/\beta = 2$) for the three patients (Cases 10–12) in Group B who received 3D conformal radiation therapy for the primary and recurrent diseases. None of the patients in Group B had symptomatic radiation necrosis. In Group A, one patient (Case 10) reportedly experienced progressive visual dysfunction after salvage CSI for the second recurrence. This can occur following multiple courses of radiation therapy and recurrence around the optic nerve. We reviewed the radiation field and dosage to elucidate the influence of multiple radiation therapy. Unfortunately, an accurate BED could not be estimated since this patient was treated with 2D radiation therapy at the initial treatment and salvage radiation therapy to the whole brain. However, the progressive visual dysfunction suggested that the former treatment had caused this symptom.

The development of new endocrine dysfunctions following irradiation depends on the patient's age at irradiation, the radiation dose to the hypothalamus and pituitary gland, and the interval after the completion of radiation therapy in patients with medulloblastoma, ependymoma, optic hypothalamic glioma and acute lymphocytic leukemia [23, 38, 39]. One young patient in Group A suffered newly developed endocrine dysfunction. Meanwhile, no endocrine dysfunction was reported in Group B. Therefore, salvage CSI after low-dose radiation therapy seems to preserve endocrine function. However, a gradual increase in endocrine dysfunction over time has been reported in a previous study, even in post-adolescent patients, so further follow-up is deemed essential [5].

High-dose radiation to the primary site results in deterioration in performance status and neurocognitive functions in childhood-onset germinoma patients [1]. To avoid this, previous research has evaluated the viability of initial treatment with reduced-dose radiation therapy. This strategy was found to successfully preserve neurocognitive functions [40]. However, no research has examined the effects of salvage CSI on neurocognitive functions in the context of recurrent disease. In Group A, salvage CSI resulted, in some patients, in additional deterioration of neurocognitive functions after damage by the initial treatment. However, in Group B patients, reduced-dose salvage CSI for recurrent disease had acceptable effects on neurocognitive function.

Comparing the MRI findings of Group A and B patients, we noted the frequent incidences of both brain atrophy and microbleeds in Group A. Recent research indicates that radiation causes dose-dependent atrophy of the hippocampus and amygdala and selective atrophy of the white matter and cortex, which are important for cognition [41–44]. This results in structural changes to the white matter, which, in turn, leads to reduced processing speed and attentional capacity [41]. These dose-dependent structural changes might explain the mechanism behind the declines in intelligence and employment status observed in Group A patients. We have previously demonstrated that radiation volume and dose are positively associated with the number of microbleeds in germinoma patients [28]. Elucidation of the relationship between microbleeds and clinical symptoms and the significance of microbleeds for the prediction of neurological deterioration remains as a challenge for future research.

LIMITATIONS

This study has some limitations. First, various treatment strategies for new and recurrent disease were adopted, especially in patients treated before the introduction of the combined platinum-based chemotherapy and reduced-dose radiation therapy protocol for newly diagnosed germinoma and combined platinum-based chemotherapy and reduced-dose salvage CSI protocol for recurrent germinoma. To evaluate the effect and safety of salvage CSI, we analyzed patient data based on the fields of the salvage radiation and the previous radiation therapy. In the future, it will be necessary to identify confounding factors in a large number of cases. Second, our patient sample was too small, and the follow-up period after salvage CSI was too short, at 10 years, to draw any definitive conclusion about the long-term effectiveness and safety of salvage CSI. Nonetheless, this report has demonstrated the range of potential complications after long-term follow-up of recurrent germinoma. Third, tumor control in non-CSI patients was not fully evaluated as the non-CSI group included only three patients. Of these three, one (Case 10) suffered recurrence outside the radiation field, but two achieved tumor control. In addition, two patients with recurrence at the primary site (Cases 14 and 15) were treated with CSI. Whether recurrence at the primary site should be treated with radiation therapy to a wider field or the local site only remains unclear. Fourth, this study did not determine the optimal salvage treatment for patients treated with high-dose radiation therapy. More extensive evaluation, including comprehensive longitudinal functional assessments, lifetime follow-up and the development of salvage therapy stratification are necessary to improve the outcomes of salvage treatment.

CONCLUSION

The present study showed that salvage CSI might achieve excellent tumor control of recurrent germinoma in patients initially treated with

low-dose radiation therapy and chemotherapy and that the safety profiles at long-term follow-up might indicate that any late adverse complications were of acceptable severity. But that salvage CSI after high-dose radiation therapy could result in reduced social status and impaired intelligence.

SUPPLEMENTARY DATA

Supplementary data is available at *RADRES Journal* online.

ACKNOWLEDGMENTS

The authors would like to thank Aries Publication Support for the English language review.

CONFLICT OF INTEREST

The authors declare no conflict of interest concerning the materials or methods used in this study or findings specified in this article.

ETHICS STATEMENT

This study was approved by the ethics board of Tohoku University Hospital (2019-1-406). The patient consent requirement was waived due to the retrospective nature of this study.

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