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Original Article

Upfront chemotherapy followed by response adaptive radiotherapy for intracranial germinoma: Prospective multicenter cohort study

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ABSTRACT

Purpose: To assess the efficacy of upfront chemotherapy followed by response-adapted reduced-dose/reduced-volume radiotherapy (RT) for intracranial germinoma.

Materials and methods: Ninety-one patients from five institutions were registered in the KSPNO G051/G081 Protocol. Germinomas were classified as solitary or multiple/disseminated diseases, and upfront chemotherapy was administered. For all patients with multiple or disseminated disease, and patients with partial response after chemotherapy, 19.5–24 Gy of craniospinal irradiation plus 10.8–19.8 Gy of tumor bed boost were planned. For patients with complete response (CR), reduced-dose RT (30.6 Gy) was planned, along with a reduced field for solitary lesions.

Results: The median patient age was 14 (range, 3–30) years. Sixty-five patients (71.4%) had a solitary lesion. The median follow-up duration was 67.9 (range, 6.6–119.3) months. Recurrence was not observed in 32 patients in the protocol compliant group. Four patients (4.4%) in the protocol non-compliant group experienced relapse after CR and one patient died of the disease. The 5-year and 7-year overall survival rates were 98.8% and 98.8%, while the corresponding event-free survival rates were 96.6% and 93.8%, respectively. All three patients with basal ganglia germinomas who were treated with local RT experienced recurrence outside the RT field. Among the 23 patients with pineal or suprasellar lesions who received whole-ventricle RT, there was no recurrence.

Conclusions: Currently used upfront chemotherapy followed by reduced-dose, reduced-volume RT appears acceptable, when whole-ventricle RT for pineal or suprasellar tumors and, at minimum, whole-brain RT for basal ganglia/thalamus lesions are applied.

Intracranial germinoma is a rare primary central nervous system (CNS) tumor with unique clinical features. It mainly occurs in adolescents and involves midline pineal or suprasellar regions. Germinomas often present as multifocal lesions or cerebrospinal fluid (CSF) disseminations, and are very radiosensitive. Therefore, with a cure rate of over 95%, craniospinal irradiation (CSI) is considered the gold-standard in the treatment of germinoma. However, chemotherapy combined with reduced radiotherapy (RT) doses and volumes has been attempted to ameliorate RT-related late toxicities; these include hormonal insufficiency, neurocognitive dysfunction, growth impairment, and second malignancies [1–3]. With improvements in the diagnostic tools used for CSF dissemination detection, such as cytology and magnetic resonance imaging (MRI), reduced-volume RT alone has also been attempted for localized germinomas without CSF dissemination [4]. Currently, there is no consensus regarding the most suitable treatment for intracranial germinomas, and diverse patterns of treatments that include whole-ventricle RT (WVRT) alone, chemotherapy with local field RT/WVRT/CSI, and CSI alone are applied according to the physicians' discretion [5,6].

Intracranial germ cell tumors are not uncommon in Korea; they comprise 1.6% of primary brain tumors in the whole population and 9.5% of the same in children [7]. Although excellent outcomes using reduced-dose CSI alone have been reported [8], upfront

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chemotherapy followed by RT using various RT doses and volumes is a popular choice for intracranial germinomas at many institutions [9].

In 2005, the Korean Society of Pediatric Neuro-Oncology (KSPNO) launched a prospective randomized trial for intracranial germinoma (KSPNO G051). The study was designed to compare the efficacy of low-dose CSI alone and upfront chemotherapy followed by RT in reduced doses and volumes. The protocol was modified in 2008 (KSPNO G081) owing to poor accrual. The KSPNO G081 was a single-arm study focusing on upfront chemotherapy followed by RT. We previously reported on 28 patients with germinomas who were enrolled in the KSPNO G051 [10]. Here, we report the outcomes of germinoma patients treated with upfront chemotherapy followed by RT according to the KSPNO G051/081 Protocol.

Materials and methods

Protocol schema

Between April 2005 and April 2011, 91 patients from five institutions were treated according to the KSPNO G051/081 Protocol (Fig. 1a). Briefly, all eligible patients were scheduled to receive four cycles of chemotherapy followed by RT. Patients with intracranial germinomas were divided into two groups, solitary and multiple/disseminated, according to the extent of the disease. Pineal and suprasellar bifocal lesions were regarded as being of multiple-site origin. RT doses and volumes were prescribed depending on the disease extent and the response to chemotherapy. All patients with multiple or disseminated diseases and a partial response (PR) to chemotherapy were scheduled to receive CSI. Patients with complete response (CR) after chemotherapy received smaller RT doses of approximately 30 Gy, as well as smaller RT volumes in cases of solitary lesions. Patients with PR after chemotherapy were prescribed RT doses and volumes that were equivalent to those applied to those in the RT-only arm of the KSPNO G051 Protocol.

Eligibility criteria

The patient eligibility criteria were as follows: (1) presence of newly diagnosed and histologically confirmed intracranial pure germinoma; (2) reception of planned therapy within 28 days of diagnostic biopsy; (3) age $\geq$3 and $\leq$30 years; (4) presence of tumor marker profiles that included serum and CSF β-human chorionic gonadotropin (HCG) levels $\leq$50 mU/mL, serum alpha-fetoprotein (AFP) levels $\leq$10 ng/mL, and CSF AFP levels $\leq$2.0 ng/mL; (5) presence of adequate bone marrow reservoir, renal function, and hepatic function; (6) reception of MRI for diagnostic purposes; and (7) provision of signed informed consent before enrollment. The protocol was approved by the institutional review board of each participating institute prior to the initiation of patient enrollment.

Diagnostic and staging work-up

Brain and spine MRI were performed for the entire study population. CSF cytology was conducted in 80 patients (87.9%); one patient (1.1%) showed positive CSF cytology. Serum tumor marker levels were measured in all patients. CSF β-HCG and AFP levels were tested in 74 (81.3%) and 80 (87.9%) patients, respectively.

Upfront chemotherapy

The compositions of the upfront chemotherapy regimens and treatment courses are shown in Fig. 1b (courses A and B, respectively). The basic principles of upfront chemotherapy were as follows: (1) it comprised four courses of chemotherapy, alternating between courses A and B, beginning with course A and ending with course B; (2) the courses were to be administered every 21 days, if possible; (3) the fourth course should comprise course B followed by a four–five week break until RT commencement.

Radiotherapy

The recommended RT doses and volumes in the protocol are shown in Fig. 1a: For a solitary lesion, reduced doses and volumes were recommended to patients with CR after chemotherapy (compared to those with PR). For disseminated disease, only dose reduction was applied to those with CR after chemotherapy.

The fractional dose was 1.5 Gy per fraction for CSI and 1.8 Gy per fraction for the reduced RT field (local RT). After CSI, computed tomography simulation for local RT was routinely performed. In terms of target volumes for local RT, either involved-field RT (IFRT) to the tumor only or WVRT followed by IFRT was allowed. In cases with severe bone marrow suppression after chemotherapy, local RT preceded CSI.

KSPNO G051

	Modality	Response to CTx	CSI	Focal RT
Solitary	RT alone		19.5	19.8 (39.3)
	CTx+RT	CR	0	30.6 (30.6)
		PR	19.5	19.8 (39.3)
Multiple or Disseminated	RT alone		24.0	16.2 (40.2)
	CTx+RT	CR	19.5	10.8 (30.3)
		PR	24.0	16.2 (40.2)

KSPNO G081

	Modality	Response to CTx	CSI	Focal RT
Solitary	CTx+RT	CR	0	30.6 (30.6)
		PR	19.5	19.8 (39.3)
Multiple or Disseminated	CTx+RT	CR	19.5	10.8 (30.3)
		PR	24.0	16.2 (40.2)

Unit: Gy, ( ): cumulative doses to primary sites

Fig. 1a. Protocol schemas of the Korean Society of Pediatric Neuro-Oncology (KSPNO) G051 and KSPNO G081 trials. CR: complete response; CSI: craniospinal irradiation; CTx: chemotherapy; PR: partial response; RT: radiotherapy.

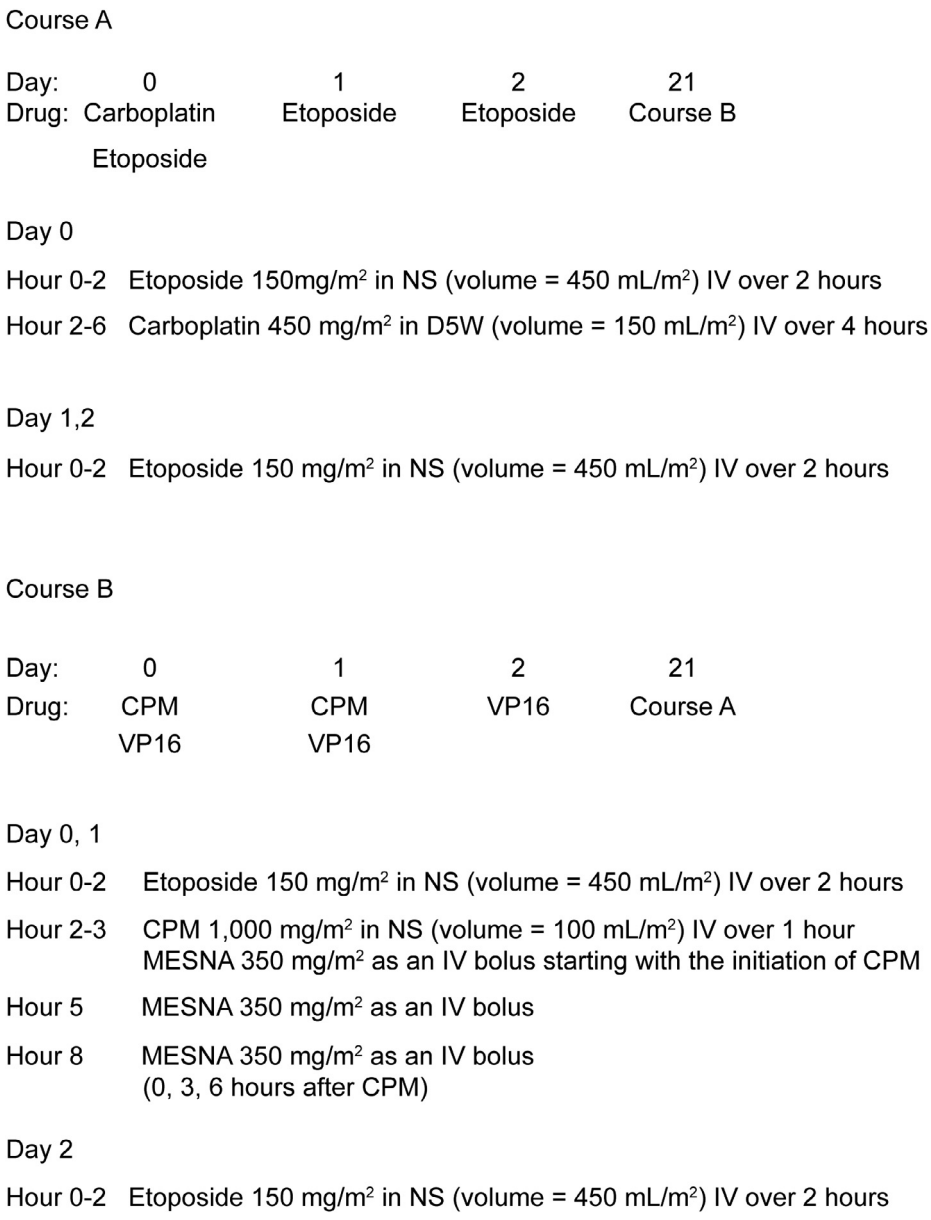

Fig. 1b. Chemotherapy schedule of KSPNO G051/G081. CPM: Cyclophosphamide.

Study endpoints, response evaluation, and toxicity evaluation

The primary endpoints were overall survival (OS) and event-free survival (EFS). OS was calculated from the date of initial pathological diagnosis to the date of last follow-up or death from any cause. EFS was calculated from the date of the initial pathological diagnosis to the date of disease progression or death. Responses after upfront chemotherapy were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.0). Acute hematologic toxicities were evaluated according to the National Cancer Institute Criteria for Adverse Events version 4.0. Neurocognitive function tests were not mandatory for this trial because the costs of the tests were not reimbursed by national health insurance or research grants.

Statistical analyses

Statistical analysis was performed using SPSS statistics version 12.0 (SPSS Inc., Chicago, IL). Comparisons between the distribution of categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test. The probabilities of OS and EFS were estimated using the Kaplan–Meier method and compared using a log-rank test. Statistical significance was defined as a p-value lower than 0.05.

Results

Patient characteristics

In all patients, the pathological diagnosis was obtained using biopsy (n = 81, 89%) or resection (n = 10, 11%; partial or total resection). The patients' median age was 14 (range, 3–30) years and 74.7% of the patients were male (Table 1). The majority of enrolled patients (71.4%) initially presented with a unifocal lesion. Among tumors of multiple origins, the most common bifocal sites were the pineal/suprasellar (9.9%) regions. Three patients (3.3%) showed tumors with origins in other bifocal areas, while tumors of multiple-site ($\geq$3) origin were observed in two (2.2%) patients. Spinal seeding metastasis was observed on imaging in 10 patients (11%) whose primary tumor sites were the pineal (n = 3), sellar/

Table 1
Patient demographics and tumor characteristics.

Characteristics		No. of patients (%)			*p*-Value
		Total (n = 91)	Compliant (n = 32)	Non-compliant (n = 59)	
Age (years)					0.140
Median (range)		14 (3–30)	15 (6–29)	14 (3–30)	
	<10	17 (18.7)	3 (9.3)	14 (23.7)	
	10–19	59 (64.8)	22 (68.8)	37 (62.7)	
	20–29	13 (14.3)	7 (21.9)	6 (10.2)	
	≥30	2 (2.2)	0 (0)	2 (3.4)	
Sex					0.583
	Male:Female	68 (74.7):23 (25.3)	25 (78.1):7 (21.9)	43 (72.9):16 (27.1)	
Primary site					
Solitary		65 (71.4)	18 (56.3)	47 (79.7)	
	Pineal	24 (26.4)	7 (38.9)	17 (36.2)	
	Sellar/Suprasellar	24 (26.4)	8 (44.4)	16 (34)	
	Basal ganglia	15 (16.5)	2 (11.1)	13 (27.7)	
	Thalamus	2 (2.2)	1 (5.6)	1 (2.1)	
Multiple/Disseminated		26 (28.6)	14 (43.7)	12 (20.3)	
	Bifocal (Pineal + Suprasellar)	9 (9.9)	4 (28.6)	5 (41.7)	
	Others	16 (17.5)	10 (71.4)	6 (50)	
	Solitary + CSF seeding	1 (1.1)	0 (0)	1 (8.3)	
Spinal seeding on MRI					0.298
	No:Yes	81 (89):10 (11)	27 (84.4):5 (15.6)	54 (91.5):5 (8.5)	
CSF cytology					0.024
	Negative:Positive:Unknown	79 (86.8):1 (1.1):11 (12.1)	32 (100):0 (0):0 (0)	47 (80):1 (1.7):11 (18.3)	

CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

suprasellar (n = 2) and pineal/thalamus (n = 2) regions, and multiple sites (n = 3). Tumor markers were not elevated above the levels indicated in the protocol, except in one patient with a solitary basal ganglia germinoma who had a slightly elevated serum β-HCG level (105.9 mU/mL). Owing to considerable protocol violations, the entire population was categorized into the protocol compliant group (those who fulfilled the protocol, including all the staging work-up) and protocol non-compliant group. The distribution of variables was not statistically different between the compliant group and non-compliant group, except in terms of CSF cytology performance (p = 0.024).

Response to upfront chemotherapy

Seventy-five patients (82.4%) completed four cycles of planned chemotherapy; seven (7.7%) did not complete planned chemotherapy owing either to early CR or toxicities. CR was achieved in 50 patients (54.9%). Response evaluation after upfront chemotherapy was possible in 86 patients (94.5%) as follow-up imaging was unavailable in five (5.5%) patients.

RT doses and volumes

The RT doses and volumes are summarized in Table 2 according to the disease extent and response after chemotherapy. CSI was likelier to be applied even in the case of solitary/CR lesions, and was ultimately administered to 55 patients (60.4%). The median CSI dose was 19.8 (range, 18–36) Gy, and the median total tumor bed dose was 39.3 (range, 27–54) Gy. In the compliant group, 12 of 18 patients with solitary lesions showed CR after chemotherapy and consequently, six PR patients with solitary lesions and 14 with disseminated disease received CSI.

For local RT, the WVRT doses were 16.2–19.8 Gy (median 19.8 Gy) in 15 solitary lesion/CR patients and 19.8–30.6 Gy (median 19.8 Gy) in six solitary lesion/PR patients. The median tumor bed doses for CR and PR after chemotherapy were 30.6 Gy and 40.2 Gy, respectively, as stated in the protocol.

Among those with solitary lesions, the RT volumes applied to the primary tumor sites were analyzed (Table 3). Among patients with pineal or sellar/suprasellar lesions, all except one received a larger RT field to at least a whole ventricle. Three of 15 patients with basal ganglia germinomas received IFRT to the tumor bed only.

Protocol compliance

In 39 (42.9%) patients, the RT protocol was adhered to, in terms of both RT dose and volume, while in 31 and 34 patients, the RT volume and RT dose, respectively, were violated; in 11 patients, CSF cytology was not performed. Finally, 32 and 59 patients were

Table 2
Radiation doses and volumes according to the disease extent and response to upfront chemotherapy.

Characteristics	RT volume* (No. of patients) Total, CSI/WB/WVRT/IFRT	Total tumor bed dose (Gy) (Median, range)	CSI dose† (Gy) (Median, range)
Group 1 (Solitary/CR)	37 17/2/15/3	30.6 (30.3–54)	19.5 (19.5–36)
Group 2 (Solitary/PR)	24 14/3/6/1	40.2 (30–54)	19.65 (19.5–24)
Group 3 (Solitary/UR)	4 2/0/2/0	30.6 (27–54)	18.75 (18–19.5)
Group 4 (Multiple‡/CR)	13 11/0/2/0	30.6 (28.8–45)	19.8 (18–36)
Group 5 (Multiple/PR)	12 10/1/1/0	40.2 (30.3–54)	23.7 (19.5–24)
Group 6 (Multiple/UR)	1 1/0/0/0	39.3	19.5

RT, radiotherapy; CSI, craniospinal irradiation; WB, whole brain; WVRT, whole ventricle radiotherapy; IFRT, involved-field radiotherapy to the tumor bed only; CR, complete response; PR, partial response; UR, unknown response.
* RT volume indicates the largest volume received.
† Among the patients who received CSI.
‡ Multiple includes disseminated disease.

Table 3
Radiotherapy target volumes in 65 patients with solitary lesions.

Primary site	No. of patients	RT volume				No. of recurrences
		IFRT*	Whole ventricle	Whole brain	CSI	
Pineal	24	1	13	2	8	0
Sellar/Suprasellar	24	0	10	0	14	0
Basal ganglia	15	3	0	3	9	4
Thalamus	2	0	0	0	2	0

RT, radiotherapy; CSI, craniospinal irradiation; IFRT, involved-field radiotherapy.
* Involved-field radiotherapy to the tumor bed only.

assigned to the protocol compliant and protocol non-compliant groups, respectively (Table 1).

OS, EFS, and recurrence demographics

The median follow-up duration was 67.9 (range, 6.6–119.3) months. A total of 11 patients (12.1%) were lost to follow-up after a median of 47.3 (range, 6.6–78.7) months following initial diagnosis; none of the patients exhibited evidence of disease at the time of their last visit. The remaining 80 patients (87.9%) were followed-up until the end of the current analysis or death. During the follow-up period, disease progression or relapse occurred in four patients (4.4%) 5.9–77 months after completion of the planned treatment following CR achievement (Table 4). The primary tumors in all four of these patients originated from the basal ganglia; they achieved CR after chemotherapy and were treated with CSI (one patient) or local RT (three patients). All patients with basal ganglia germinoma who were treated with local RT experienced disease recurrence outside the RT field (Table 3). Among these four patients, three were successfully salvaged and were alive 91, 98.7, and 117.6 months, respectively, after their initial diagnosis without evidence of disease; the remaining patient died without any salvage treatment after recurrence. The 5-year and 7-year OS rates were 98.8% and 98.8%, and the 5-year and 7-year EFS rates were 96.6% and 93.8%, respectively (Fig. 2). All four patients with recurrence belonged to the non-compliant group; two showed RT dose violation and one showed both RT dose and volume violation. In one patient, CSF cytology was not performed. The OS rates were not statistically different between the protocol compliant group and protocol non-compliant group ($p = 0.453$). Although the protocol compliant group showed superior EFS rates compared to the

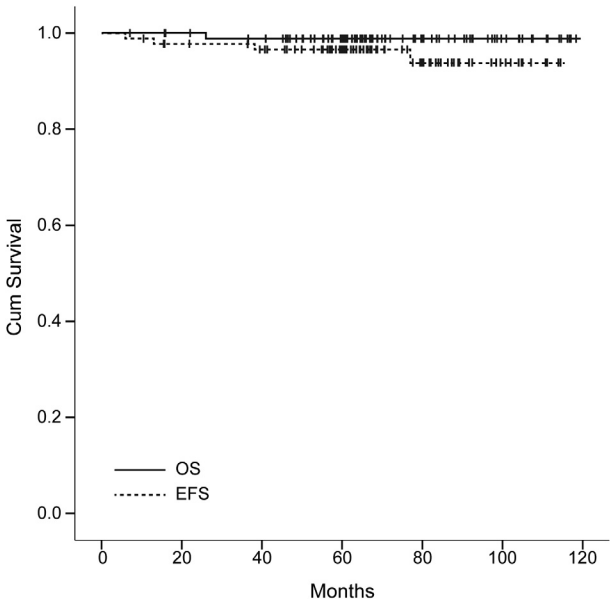

Fig. 2. Kaplan–Meier survival curves.

Table 4
Detailed characteristics of the recurrence cases ($n = 4$).

Characteristics	Pt 1	Pt 2	Pt 3	Pt 4
At initial diagnosis				
Sex	Male	Male	Male	Male
Age (years)	9	15	9	9
Primary site	Rt. basal ganglia	Both basal ganglia	Rt. Basal ganglia	Lt. basal ganglia
Spine MRI	Negative	Negative	Negative	Negative
CSF cytology	Negative	Negative	Negative	NA
Serum/CSF β-HCG	Normal/Normal	Normal/Normal	Normal/Normal	105.9/NA
Serum/CSF AFP	Normal/Normal	Normal/Normal	Normal/Normal	Normal/NA
CTx-cycle	4	4	4	4
CTx-response	CR	CR	CR	CR
CSI dose (Gy)	0	23.4	0	0
Tumor bed dose (Gy)	39.6	50.4	39.6	30.6
At recurrence				
Relapse site	Lt. temporal lobe	Lt. side of pons	Rt. frontal lobe/Ant. temporal lobe	Rt. basal ganglia
Biopsy status	Positive	NA	NA	Positive
Spine MRI	Negative	Negative	Negative	Negative
CSF cytology	Negative	Negative	Negative	NA
Serum/CSF β-HCG	89/471	Normal/Normal	Normal/65.5	Normal/NA
Serum/CSF AFP	Normal/Normal	Normal/Normal	Normal/Normal	Normal/NA
RFI (mo)	13	5.9	38.2	77
Salvage treatment	No	CTx → CR	HDCTx, PBSCT, CSI 23.4 Gy → CR	CTx + CSI
Last status (mo)	DWD (25.8)	NED (98.7)	NED (117.6)	NED (91)

RFI, relapse-free interval; NA, not available; CTx, chemotherapy; HDCTx, high-dose chemotherapy; PBSCT, peripheral blood stem cell transplantation; CSI, craniospinal irradiation; CR, complete response; DWD, dead with disease; NED, no evidence of disease; MRI, magnetic resonance imaging; β-HCG, β-human chorionic gonadotropin; AFP, alpha-fetoprotein.

protocol non-compliant group, the result was not statistically significant ($p = 0.121$) (supplementary Figs. 1 and 2).

Toxicity following neoadjuvant chemotherapy

Acute hematologic toxicities during chemotherapy were evaluated in 90 patients (98.9%). Grade ≥3 anemia, leukopenia, neutropenia, and thrombocytopenia developed in 37 (40.7%), 89 (97.8%), 89 (97.8%), and 61 (67.1%) of the patients, respectively.

Discussion

Although chemotherapy followed by reduced-volume RT trials has been shown to produce fairly good survival outcomes [11], the optimum RT doses and volumes in the setting of combined chemotherapy and RT have not been defined. The protocol used in the current study resulted in excellent survival outcomes and showed that the administration of a proper RT volume can lead to efficient germinoma management.

The RT doses administered to patients have gradually reduced over time. A single-institution study in Korea revealed that low-dose CSI (19.5–21 Gy of CSI followed by 19.8 Gy to the tumor area) led to 100% survival, suggesting that the RT dose to the tumor site can be reduced to less than 40 Gy, and that to the CSF space to less than 20 Gy [8]. These dosing schemes were the basis of our current trial and were recommended for patients who did not achieve CR after upfront chemotherapy.

Through this multicenter clinical trial, we confirmed that lower-dose RT could control germinomas in combined modality treatments. No primary-site recurrence was observed in the 29 patients with CR who received ≤30.6 Gy. Further, no primary-site recurrence was noted in the 21 patients with PR who received ≤40.2 Gy. This raised the possibility of further reducing RT doses. In Japan, 24 Gy is used for patients with upfront chemotherapy [12]. However, in our study, one patient who received 23.4 Gy experienced recurrence in an area that was not involved at diagnosis. In Taiwan, 30 Gy was suggested for RT-only settings [4]. Thus, the optimal RT dose is still controversial in both combined modality and RT-only settings.

With respect to RT volume, IFRT to the tumor area after successful chemotherapy resulted in frequent recurrence outside the RT field, mainly along the ventricles [13,14]. Thereafter, WVRT was suggested as an optimal RT volume, even for patients with CR after chemotherapy. In this study, no such relapse occurred in 48 patients with solitary pineal or suprasellar lesions; 48% of these patients (including six with PR after chemotherapy) received WVRT. Therefore, WVRT provides an optimal RT volume for solitary pineal or suprasellar lesions, even in patients with PR after upfront chemotherapy.

In patients with germinomas originating from the basal ganglia or thalamus, IFRT to the tumor area alone after chemotherapy resulted in high recurrence rates. Among the 15 patients with basal ganglia germinoma, three received IFRT and all experienced recurrence outside the RT field. The remaining 12 patients received CSI or whole-brain RT. Among them, one patient who received 23.4 Gy of CSI experienced recurrence outside the primary site boost RT field. All patients with recurrence had previously achieved CR after upfront chemotherapy, suggesting that the chemotherapy used was insufficient in the control of microscopic tumors outside the RT field. Compared to pineal and suprasellar germinomas, those arising from the basal ganglia have unique clinical features. They infiltrate the brain parenchyma and cause atrophic changes with neurologic deficits. Furthermore, the radiologic findings are variable, ranging from subtle parenchyma changes to contrast-enhanced masses with or without cystic lesions, and (often) not-well defined extensions [15,16]. Therefore, whole-brain RT or CSI should be considered for basal ganglia germinomas [16].

All disseminated disease types, including bifocal lesions, should receive CSI according to the protocol. The RT doses for patients who achieved CR after chemotherapy were slightly lower than those in the RT-only arm, as per the KSPNO G051 Protocol (19.8 Gy vs. 24 Gy for CSI and 30.6 Gy vs. 40.2 Gy to the tumor area, respectively). Patients with PR after chemotherapy who later received additional full-dose CSI likely underwent chemotherapy unnecessarily. In our cohort, 12 of 26 patients (46.1%) showed PR after chemotherapy and ultimately received CSI with the same RT doses as those designated to the RT-only protocol. Considering the disadvantages of chemotherapy, the potential detrimental effects of slightly higher RT doses should be carefully assessed. In the SIOP CNS GCT 96 trial, 45 patients with metastatic disease received 24 Gy of CSI followed by a 16-Gy boost to the tumor area; 17 of these patients received additional chemotherapy before CSI and did not experience recurrence. It was concluded that reduced-dose CSI alone is effective against metastatic disease [1].

The strengths of this study are its prospective design and the inclusion of a relatively large number of patients, all of whom had pathologically proven pure germinomas. A limitation of the study is the poor protocol compliance. Most of the protocol violations pertained to RT doses and volumes that were greater than those specified in the protocol. These violations may have improved survival outcomes. A larger number of recurrences may have occurred if all the solitary/CR patients had received local RT per the protocol, rather than CSI.

Nonetheless, based on a subgroup analysis of patients with protocol adherence, we were still able to obtain some important findings regarding proper RT doses and volumes: Relapse rates can be reduced through RT-volume modification, which should include the whole ventricle for localized pineal or suprasellar tumors and at least the whole brain for localized basal ganglia/thalamus lesions. For disseminated disease, CSI alone is appropriate. This combined strategy should be compared with reduced-dose, reduced-volume RT alone in future clinical trials, and its superiority with respect to long-term toxicities as well as survival outcomes should be verified before its adoption as a standard treatment for germinomas.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.06.002.

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