BMC Cancer

SYSTEMATIC REVIEW Open Access

Optimal treatment approach for intracranial germinoma: a systematic review and meta-analysis

Zhirui Zhou[1,2,10*†], Jiabing Liu[1,2†], Qi Yue[2,3†], Lingxiao Chen[4], Xiwei Zhang[5], Xin Lin[6], Lin Zheng[7], Enmin Wang[2,8], Yang Wang[1,2,11*] and Ying Mao[2,3,9*]

Abstract

Background To determine the optimal treatment modality for intracranial germinoma (IG).

Materials and methods A search of Medline, Embase, Web of Science and Cochrane Library was conducted up to April, 2024. Pooled risk ratio (RR) and 95% confidence interval (CI) were calculated. Subgroup analysis was applied according to radiotherapy (RT) alone or with chemotherapy (CTx).

Results Total 37 studies were included in systematic review. Most IG patients were treated with biopsy or resection followed by RT with or without CTx. Prognosis of IG patients with different surgical resection is similar. Meta-analyses demonstrated focal field RT were with higher recurrence rate compared with craniospinal irradiation (CSI) [RR = 7.128, 95% CI (5.083, 9.995)], whole-brain RT (WBRT) [RR = 4.094, 95% CI (2.923, 5.735)] or whole-ventricle RT (WVRT) [RR = 3.361, 95% CI (2.126, 5.312)]; both WBRT and WVRT were also with higher recurrence compared with CSI; but no significant difference in recurrence and mortality between WVRT and WBRT. Total 24 studies reported treatment-related acute and/or late toxicity, combination CTx increased acute toxic, and expanded RT field and/or dose increased late toxicity.

Conclusion Based on our findings, focal field RT is not recommended regardless of whether combined with CTx for intracranial pure germinoma. Although CSI is associated with better local control than other reduced-field RT, considering the potential toxicity and pattern of relapse, whole ventricles irradiation is more reasonable for localized or nonmetastatic germinoma. Reduced-dose CSI with or without chemotherapy is effective in metastatic or disseminated IG.

Keywords Intracranial germinoma, Surgical resection, Radiotherapy, Chemotherapy, Meta-analysis

†Zhirui Zhou, Jiabing Liu, and Qi Yue contributed equally to this work.

*Correspondence:
Zhirui Zhou
zzr3711@163.com
Yang Wang
Janetcyj@163.com
Ying Mao
maoying@fudan.edu.cn

Full list of author information is available at the end of the article

Introduction

Intracranial germinoma (IG) is a rare tumor of the central nervous system (CNS) that occurs worldwide. The incidence of germinomas has been considered to be higher in East Asia than in Western countries, but a recent study has shown that the incidence of these tumors is similar between Japan and the United States [1]. Intracranial germinomas most commonly occur in childhood and adolescence, with 35–40% of cases occurring before the age of 14 years and 90% of patients diagnosed before the age of 20 years [1]. Sellar, pineal gland, and basal ganglia regions are the most commonly involved areas of germinomas. IG are highly radiosensitive and chemosensitive, with a tendency to spread via cerebrospinal fluid (CSF) [2]. In recent decades, radiotherapy and/or chemotherapy plays an important role in IG treatment. Owing to the high sensitivity of germinoma to radiotherapy, the 5-year overall survival rate is more than 90% [2, 3].

Although radiotherapy is essential to the management of intracranial germ cell tumors, the ideal radiation field and dose remain controversial. To date, various treatments, such as whole ventricle (WV) or whole brain radiotherapy (WBRT) or craniospinal irradiation (CSI) alone, chemotherapy (CTx) followed by focal RT/WVRT/WBRT/CSI, have been applied per physicians' discretion [4, 5]. CSI used to be the standard of care, with this treatment approach, the majority of patients have been cured. Concerns have long been raised about the potential adverse effects of CSI [6], many studies have explored reduced-field irradiation and showed that CSI could be spared in patients with localized IG with chemotherapy support [7, 8]. A multi-institutional retrospective study, comparing the patterns of treatment and reporting clinical outcomes from the various intervention strategies, showing that focal field RT having the worst outcome, whereas chemotherapy usage had no impact on survival [9]. To further define the optimal treatment volume, a study on relapse patterns after focal RT was conducted in patients with localized intracranial germinoma [10]. Results from these studies showed that in patients with sellar or pineal gland germinoma, the periventricular areas were at risk of recurrence, which warranted the use of whole-ventricle irradiation.

However, areas of controversies and literature gaps still exist. Optimal treatment approach for intracranial germinoma, such as surgical resection method, radiotherapy volume, dose, and the necessity for adjuvant CTx, remain unclear. Here, we aimed to investigate the pattern of disease relapse and determine the optimal treatment strategy for IG by analyzing patient outcomes for various approaches. This study mainly answers two questions: is there any difference in recurrence rate among different radiotherapy volume? Does combination chemotherapy exempt craniospinal irradiation? To our knowledge, this systematic review and meta-analysis involves the largest number of studies and intracranial germinoma patients, represents the highest level of evidence available regarding the efficacy and safety of different treatment modalities for IG. Our report may suggest that future directions for the choice of optimal treatment approach for intracranial germinoma.

Materials and methods

Study eligibility

This study was conducted following a protocol and adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) updated statement [11] and Assessing the Methodological Quality of Systematic Reviews (AMSTAR) guideline [12]. This systematic review was registered in PROSPERO (No. CRD42024540172). Two reviewers worked independently to identify original study eligible for further review by screening abstract and title. Disagreement was settled by consensus, otherwise one more author was added to reach the consensus.

Inclusion criteria were as follows: (1) patients with histologically proven intracranial pure germinoma. Patients with a clinical diagnosis based on neuroimaging characteristics and response to RT were allowed to be included, alpha-fetoprotein (AFP) levels had to be ≤ 25 ng/mL and human chorionic gonadotropin (HCG) levels ≤ 50 IU/L to treat for germinomas; (2) radiotherapy with or without chemotherapy was as first-line treatment; (3) prospective or retrospective controlled studies were enrolled; (4) at least two of these four RT volumes (Focal, WV, WB, CSI with or without boost to primary lesion) were included in the study; (5) the main outcome of interest focus on relapse and death events; (6) for duplicate articles, only the one with largest patient samples and/or recently published was included; (7) sample size of intracranial germinoma more than 20.

Exclusion criteria were as following: (1) non-germinomatous germ cell tumors (NGGCT); (2) uncontrolled studies, such case report, case series, etc.; (3) given information was insufficient to extract the required data; (4) non-original study, such as review, survey, etc.; (5) conventional fraction dose less than 1.5 Gy per fraction, hypofractionated radiotherapy or radiosurgery.

Search strategy

A search of Medline, Embase, Web of Science, and Cochrane Library was conducted from database construction to April, 2024. MeSH or Emtree terms combined free terms were used: "central nerve system", "intracranial germinoma", "germinoma", "germinomatous", "surgery", "resection", "chemotherapy", "chemoradiotherapy", "radiotherapy", "radiation therapy", "irradiation", "radiotherapy field", "focal radiotherapy", "whole ventricle

radiotherapy", "whole brain radiotherapy", "craniospinal irradiation". References of included studies were used to locate potentially eligible articles. Furthermore, abstracts published in major academic conferences were checked. Research works were conducted independently by two reviewers first, and then the full articles chosen valuable were carefully reviewed. No language restrictions were applied.

Data extraction

Following information was extracted from each article: participant's eligibility, study design, baseline characteristics, radiotherapy, chemotherapy, surgical resection, duration of follow up, number of events and patients in each intervention group, sample size, etc. Outcomes regard to recurrence, mortality events and acute/late toxicity. If the results were reported in multiple publications, we would extract the data from all the publications.

Risk of bias assessment

Non-randomized controlled trials were evaluated according to the Methodological Index for non-Randomized Studies (MINORS) [13] and Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) [14].

Statistical analysis

All statistical analyses were performed using StataMP 13.1 (StataCorp, Texas, USA). Dichotomous data using pooled risk ratio (RR) and 95% confidence intervals (CI) was calculated. Cochran's Q-test was used for testing heterogeneity between studies. If heterogeneity was not present ($P > 0.10$, $I^2 < 50\%$), both fixed-effect model (Mantel-Haenzel method) and random-effect model (DerSimonian&Laird method) were adopted for analysis, otherwise, random-effect model would be employed. In order to further explore the difference of prognosis between different radiation fields in radiotherapy alone or combined with chemotherapy, then we performed subgroup analysis according to these two kinds of treatment strategies. In the case of excessive heterogeneity, descriptive analysis rather than meta-analysis would be employed. For studies where no events were observed in one arm, add a fixed value 0.5 to zero cell; exclude studies from the meta-analysis where there are no events in both arms. P value < 0.05 was defined as statistically significant.

Results

Study selection and baseline characteristics

Finally, 54 full-text from 37 studies [7, 9, 15–49] (3 prospective and 34 retrospective studies), total 3163 IG patients, met the inclusion criteria and were included in systematic review; 53 full-text from 36 studies [7, 9, 15–17, 19–49], total 2951 intracranial germinoma patients, were finally included in meta-analysis. The PRISMA flow diagram was shown in Fig. 1. Baseline characteristics of the included studies were summarized in Table 1.

Risk of bias assessment

All 37 studies were evaluated according to the MINORS index and ROBINS-I assessment tool, the scores and risk level were showed in Supplementary Table 1. The main limitations of included studies were as following: only three studies were prospective studies, and the rest were retrospective studies; most of the included studies did not control for confounding factors, such as location of the lesion and presence or absence of metastasis, thus, there was a possibility of selection bias.

Surgical resection

Most patients were treated with biopsy followed by RT with or without CTx, and some patients treated with resection followed by RT with or without CTx. Among them, a very small number of patients can achieve gross total resection (Table 1). This systematic review showed that pure germinoma have good prognosis and the 5-year overall survival rate is more than 90%; prognosis of patients with different surgical resection methods is similar (Table 1). Given the high sensitivity of the IG disease to radiotherapy and/or chemotherapy, the good prognosis, and the fact that the disease is often located near the midline, it is difficult to achieve safe gross total resection.

Meta-analysis of different radiation volume

Recurrence in full-set

Thirty studies with 1512 patients assessed the recurrence rate of focal RT vs. CSI. Pooled RR indicated focal RT were with higher recurrence compared with CSI [RR=7.128, 95% CI (5.083, 9.995), P=0.000] (Fig. 2A). Nineteen studies with 1061 patients were included in meta-analysis to calculate recurrence rate of WVRT vs. CSI. Pooled RR indicated that WVRT were with higher recurrence in comparison with CSI [RR=2.771, 95% CI (1.375, 5.584), P=0.004] (Fig. 2B). Thirty studies with 1530 IG patients assessed the recurrence rate of WBRT vs. CSI. Pooled RR manifested WBRT were with higher recurrence compared with CSI [RR=2.397, 95% CI (1.388, 4.140), P=0.002] (Fig. 2C). Nineteen studies with 778 patients were included in meta-analysis to calculate recurrence rate of focal RT vs. WVRT. Pooled RR indicated that focal field RT were with higher recurrence in comparison with WVRT [RR=3.361, 95% CI (2.126, 5.312), P=0.000] (Fig. 2D). Twenty-six studies with 915 patients were included in meta-analysis to evaluate recurrence rate of focal RT vs. WBRT. Pooled RR also indicated that focal field RT were with higher recurrence in comparison with WBRT [RR=4.094, 95% CI (2.923, 5.735), P=0.000] (Fig. 2E). Nineteen studies with 730 patients

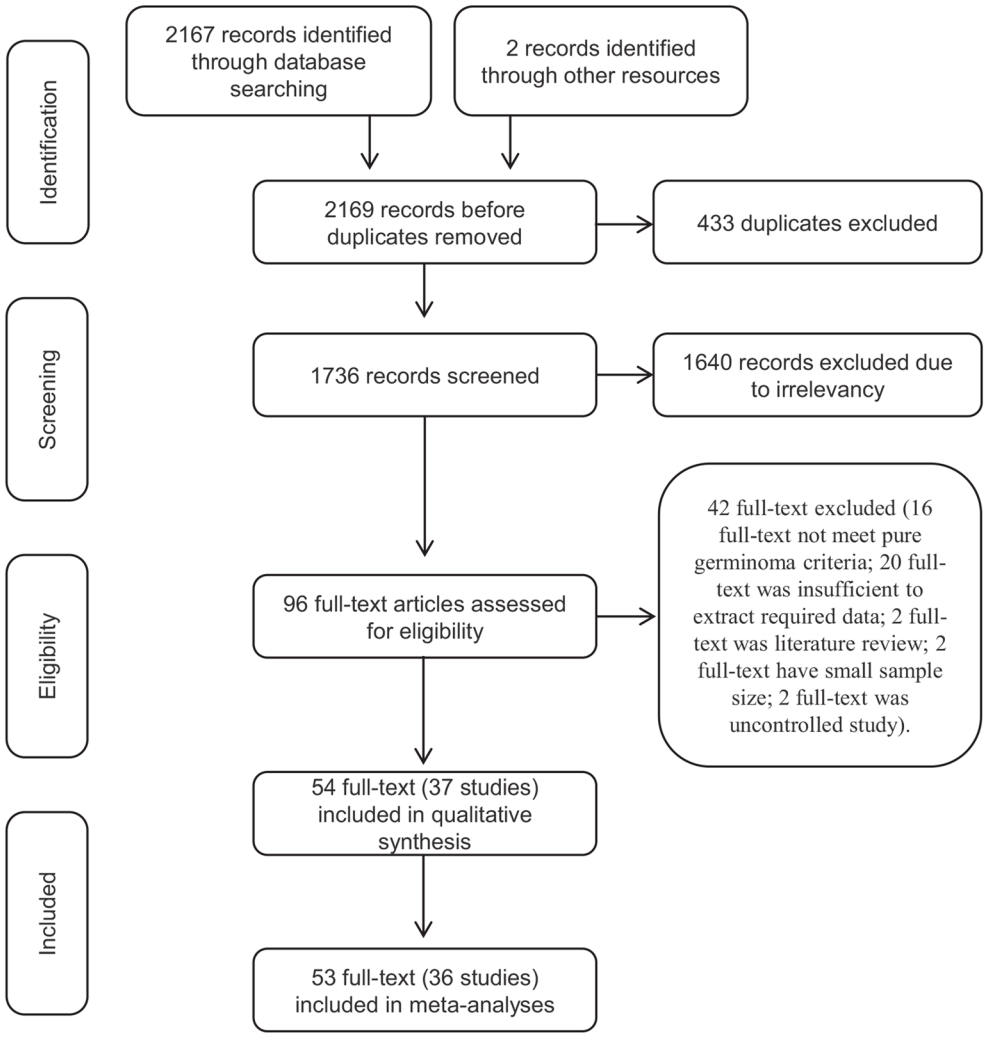

Fig. 1 Flowchart depicting study selection

were included in meta-analysis to evaluate recurrence of WVRT vs. WBRT. Pooled RR manifested no significant difference between WVRT and WBRT [RR=1.444, 95% CI (0.796, 2.619), P=0.227] (Fig. 2F). In these meta-analyses, no obvious heterogeneity was found, both random and fixed effect model were employed, and more detailed meta-analyses results were shown in Table 2.

Mortality in full-set

Twenty-three studies with 1204 patients assessed the mortality of focal RT vs. CSI. Pooled RR manifested focal RT were with higher mortality compared with CSI [RR=3.134, 95% CI (1.804, 5.446), P=0.000] (Fig. 3A). Seventeen studies with 838 patients were included into this meta-analysis to calculate mortality of WVRT vs. CSI. Pooled RR indicated that no significant difference between WVRT and CSI [RR=1.311, 95% CI (0.425, 4.047), P=0.638] (Fig. 3B). Twenty-two studies with 1046 patients assessed the mortality of WBRT vs. CSI. Pooled RR showed that there was borderline significant difference between WBRT and CSI [RR=2.103, 95% CI (0.980, 4.514), P=0.056] (Fig. 3C). Seventeen studies with 692 patients were included in meta-analysis to calculate mortality of focal RT vs. WVRT. Pooled RR indicated that focal field RT were with higher mortality compared with WVRT [RR=2.559, 95% CI (1.263, 5.185), P=0.009] (Fig. 3D). Twenty-one studies with 708 patients were included in this meta-analysis to evaluate mortality of focal RT vs. WBRT. Pooled RR also indicated that focal RT were with higher mortality in the comparison with WBRT [RR=2.635, 95% CI (1.504, 4.614), P=0.001] (Fig. 3E). Seventeen studies with 515 IG patients were included in the meta-analysis to evaluate mortality of WVRT vs. WBRT. Pooled RR manifested no significant difference between WVRT and WBRT [RR=0.533, 95% CI (0.184, 1.541), P=0.245] (Fig. 3F). In these meta-analyses, no obvious heterogeneity was found (except for WVRT vs. CSI, I^2=51.6%, τ^2= 1.4156), the random

Table 1 Baseline characteristics of included studies

Study Name/ AuthorYear	Publish Year	Sample Size (*N*)	Study Design	Tumor Extension (*M*)	Interventions (*N*)	RT Field (*N*)	Dose (boost) (Gy)	Chemothrapy (*N*)	Surgery (*N*)	Outcomes	Gender M/F (*N*)	Age (years)	Country/ Region	Follow-up (months)
Aoyama 1998	*1998*	41	multi-institutional retrospective study	localized:31, multi-focal:7, CSF dissemination:3	radiotherapy:41; biopsy/resection:41; chemotherapy:13	focal:8; whole-brain:10; craniospinal:23	primary sites: median 46 Gy; whole-brain: median 32 Gy; spinal: median 30 Gy	with/without platinum-compound after RT:5/4, with platinum-compound before RT:3, simultaneous without platinum-compound:1	biopsy: 17, partial resection:19, total resection:5	RFS:10-year,90%,76% and 22% for craniospinal, whole-brain and local field; OS and CSS:5-and 10-year,91/94% and 87/90%.	M/F:33/8	less than 16/ more than 16:22/19	Northern Japan	median 78 months
Byun 2020	*2020*	213	single-center retrospective study	solitary:151, bifocal:32, multifocal/disseminated:30	radiotherapy:210; biopsy/resection:126; chemotherapy:76	focal:29; whole-brain/ventricle:51; craniospinal:130	primary sites:30 to 59 Gy; neuraxis:18 to 36 Gy	CTx+RT:73, CTx:3	biopsy: 97, partial/subtotal resection:24/2, total resection:3,	DFS:10 year 91.6%; OS:10 year 95.6%; toxicity.	M/F:163/50	median (range):16.2(3.5–66.0)	Korea	median 141 months (range 0.4–518)
SIOP CNS GCT 96	*2013*	235	multi-institutional non-randomized study	localized 190: 94 pineal, 53 supra-/irasellar, 32 bifocal, 11 other sites. metastatic:45	radiotherapy:235; biopsy/resection:232; chemotherapy:110	focal:65; craniospinal:125	primary sites:40 Gy; neuraxis:24 Gy	CTx+RT:65, carboplatin/etoposide alternating with etoposide/ifosfamide*2	stereotactic biopsy:103, partial/open biopsy:107, total resection:23,	EFS:5 year, CSI vs. focal, 94% vs. 88%; OS:5 year, CSI vs. focal, 95% vs. 96%; PFS:5 year, CSI vs. focal, 97% vs. 88%; toxicity.	M/F:176/59	median (range):13(4–42)	International	median 72 months (range 32–168)
Chen 2012	*2012*	80	single-center retrospective study	localized 62:sellar and suprasellar:23, pineal:14,thalamus/basal ganglion:22/3; multi-focal:12; CSF dissemination:6	radiotherapy:80; biopsy/resection:50; chemotherapy:29	focal:27; whole-brain/ventricle:8/31; craniospinal:14	primary sites: before 1990s median 50 Gy(range,40.5–54),mid-to late 1990s median 30 Gy(range,28–50),early 2000s median 30 Gy(range,29.3–50); whole-brain/ventricle: before 1990s WBI median 29.4 Gy(range,8-30.9),early 2000s WVI 24.5 Gy(range,23.3–30); neuraxis: before 1990s median 27 Gy(range,25.5–28.5)	CTx+RT:29, 6 to 8 courses of the VBEP	pathological/ clinical:44/30, CSF cytology:6	RFS:5-year, CSI, WBI, WVI, and focal, 100%, 85.7%, 100%, and 84.6%; OS:5-year, CSI, WBI, WVI, and focal, 100%, 83.3%, 100%, and 87.9%; toxicity.	M/F:57/17	median (range):12(5–20)	Taipei	median 82.3 months range(5.1-236.8)

Table 1 (continued)

Study Name/ AuthorYear	Pub-lish Year	Sample Size (*N*)	Study De-sign	Tumor Extension (*N*)	Inter-ven-tions (*N*)	RT Field (*N*)	Dose (boost) (Gy)	Chemothrapy (*N*)	Surgery (*N*)	Outcomes	Gender M/F (*N*)	Age (years)	Coun-try/ Re-gion	Follow-up (months)
Eom 2008	*2008*	81	sin-gle-center retro-spec-tive study	localized:60; CSF dissemination:21	radio-thera-py:81; biopsy/ resec-tion:81; chemo-thera-py:42	focal:23; whole-brain/ventricle: unclear; craniospinal:52	primary sites: RT median 54 Gy(range,40–56), RT + CTx median 50 Gy(range,36–54); neuraxis: RT median 21 Gy(range,13–45) negative seeding, median 36 Gy(range,24–45) positive seeding.	CTx + RT:42, 2 cycles BEP/EP 29, 5 cycles VCEP 10, other 2	stereotactic biopsy 27, endoscopic/open biopsy 20/10, partial removal 12, subtotal removal 9, gross total removal 3	Response to RT/ CRT, RFS,5 year 100.0% RT and 88.1% CRT; OS,5 year 100% RT and 92.9% CRT; OS,10 year 92.5% RT and 92.9% CRT; toxicity.	M/F: RT 27/12, CRT 38/4	median (range): RT 14.6(8–41), CRT 17.5(8–44)	Korea	median 68 months range(8-231)
Foo 2023	*2023*	46	sin-gle-center retro-spec-tive study	suprasellar 11, pineal 10, bifocal 3, basal ganglia 1, metastatic 4.	radio-thera-py:29; biopsy/ resec-tion:23; chemo-thera-py:29	whole ventricle:23; whole-brain:5; craniospinal:1	whole-ventricle:23.4 Gy(no boost); whole-brain:23.4 Gy(no boost); craniospinal:23.4 Gy(no boost)	3–4 cycles carbopla-tin + etoposide 22, carboplatin/eto-poside alternating with etoposide/ ifosfamide*2: 6, 4 cycles carbo-platin + weekly vinblastine:1	biopsy 22, debulking 1	PFS, 5-year 91%; OS: 5-year 100%	M/F:14/15	median (range):12.8(6.2–17.3)	Cana-da	median 63 months range(9-187)
Graham 2021	*2021*	43	multi-insti-tu-tional retro-spec-tive study	basal ganglia/bilateral/ extension 28/4/10, thalamic/bilateral/extension 23/8/11.	radio-thera-py:38; biopsy/ resec-tion:38; chemo-thera-py:38	focal:9; whole-brain/ ventricle:8/15; craniospinal:6; boost:23	focal RT (median 36 Gy); WVI (median 23.4 Gy/Gy[RBE]), boost to 36–45 Gy; WBI (median 23.4 Gy/Gy[RBE]), boost to 36–45 Gy; CSI (median 22.4 Gy/Gy[RBE]), boost to 30–546 Gy.	CTx:38 pts, Carbo, Etop/Carbo, Etop, Cisplatin, Cyclo/ Carbo, Etop, Ifos/ Carbo, Etop, Bleomycin/ Cisplatin, Etop, VBL/ Etop, Cisplatin, Cyclo, VCR	biopsy 35 pts, subtotal resection 2 pts, gross total resection 1 pts	EFS,5-and 10-year, 85.8% and 81.0%; OS,5-and 10-year,100% and 95.5%; 2pts CTx relapse, 1pt died from unrelated cause; toxicity.	M/F:36/7	median (range):13.2(4.8–31)	Aus-tralia, Brazil, Can-ada, USA	median 87 months
Haddock 1997	*1997*	48	multi-insti-tu-tional retro-spec-tive study	suprasella 25, pineal 15, multiple 2, other 6.	radio-thera-py:48; biopsy/ resec-tion:47; chemo-thera-py:5	prior- 1973 plus after 1973: partial brain:13 + 11, whole-brain:1 + 10, craniospinal:2 + 10	primary: median 44 Gy(7.44–59.40); whole-brain: median 30 Gy(3.6–40); craniospinal: median 27.75 Gy(16.58–32.82).	CTx:5 pts, cisplati-num + etoposide prior to RT	biopsy 28 pts, subtotal resection 16 pts, gross total resection 3 pts, CSF positive 1 pts	OS,5-and 10-year, entire,80%; OS,5-and 10-year, prior/after 1973,63%/91%; DFS,5-and 10-year, prior/after 1973,62%/70% and 63%; toxicity.	M/F:39/9	median (range):17(6–44)	USA	median 66 months range(4-444)
Harden-bergh 1997	*1997*	40 *lower dose: 32*	sin-gle-center retro-spec-tive study	suprasella 12, pineal 11, multiple midline 17.	radio-thera-py:40; biopsy/ resec-tion:17; chemo-thera-py:5	focal:14; whole-brain:9; craniospinal:9	primary site: median 52 Gy(44.5–59.5 Gy); whole-brain: median 32.4 Gy(15–44.37 Gy); craniospinal: median 25 Gy(18.7–37.5 Gy).	cisplatin-base 4, intrathecal metho-trexate 1.	biopsy 17 pts	DFS,5-year,97%; OS,5-year,97%; toxicity.	M/F:26/14	median (range):14(0.5–31)	USA	median 62 months range(3-226)

Table 1 (continued)

Study Name/ AuthorYear	Publish Year	Sample Size (*N*)	Study Design	Tumor Extension (*N*)	Interventions (*N*)	RT Field (*N*)	Dose (boost) (Gy)	Chemothrapy (*N*)	Surgery (*N*)	Outcomes	Gender M/F (*N*)	Age (years)	Country/ Region	Follow-up (months)
Jensen 2010	*2010*	59	single-center retrospective study	CRT/RT: suprasellar 9/18, pineal 8/7,multiple 6/5, spinal or positive CSF 5/1.	radiotherapy:59; biopsy/resection:17; chemotherapy:54	CRT/RT: focal 17/9, whole-brain 0/8, whole-ventricle 1/0, craniospinal 10/9, unknown 0/5.	primary site: range(30.3–56 Gy); whole-ventricle:23.4 Gy; whole-brain: range(10.8–40 Gy); craniospinal: range(19.5–40 Gy).	cisplatin etoposide:24, carboplatin/carmustine/etoposide/streptozotocin:2, bleomycin/cisplatin/etoposide:1, bleomycin/cisplatin/etoposide:1	CRT/RT: resection 6/11 pts, biopsy 20/17 pts, none 2/3 pts	CRT: freedom from progression (FFP), 5-and 10-year,88% and 80%; OS:5-and 10-year,100%; DFS:5-and 10-year,80% and 71% for local-fields vs. 100% for extensive-fields. RT: FFP 5-and 10-year,82%; DFS:5-and 10-year,79% and 75%, 44% for local fields vs. 100% for extensive fields; OS:5-and 10-year,93% and 90%.	CRT: M/F:23/5 RT: M/F:23/8	CRT: median (range):16(9–42) RT: median (range):19(5–35)	USA	CRT/RT: median 79.2 months range(9.6-196.8)/ median 174 months range(10.8-308.4)
Jinguji 2013	*2013*	46 *RT/CRT:38/7*	single-center retrospective study	localized:30, multifocal or disseminated:16	radiotherapy:45; biopsy/resection:46; chemotherapy:8	CRT/RT: focal:3/0, whole-brain:2/6, craniospinal:2/32.	1.6–2.0 Gy/F, once a day, 35 pts: primary site: mean 49.9 Gy(44.7–52.8 Gy), whole-brain: mean 25.9 Gy(18–30.4 Gy), craniospinal: mean 25.9 Gy(23.8–30.6 Gy). 1.2 Gy/F, twice a day, 7 pts: primary site: mean 49.4 Gy(45.6–52.5 Gy), whole-brain: mean 32.1 Gy(28.8–36 Gy), craniospinal: mean 30.7 Gy(28.8–36 Gy).	3–6 cycles CTx: CARE(carboplatin 450 mg/m2 and etoposide 150 mg/m2); PE(cisplatin 20 mg/m2 and etoposide 100 mg/m2).	biopsy 25 pts, partial resection 10 pts, subtotal resection 8 pts, gross total resection 3 pts	OS:5-, 10-, 15-year 100%, 93.3%, and 88.2%; RFS:5-,10-, 15-year 95.7%,89.3%, and 84.3%; toxicity.	M/F:35/11	range: (5–43)	Japan	median 125 months range(25–235)
Joo 2014	*2014*	72	single-center retrospective study	pineal gland 34, suprasellar 25, basal ganglia 5, multifocal 6, other 2	radiotherapy:72; biopsy/resection: unknow; chemotherapy:72	after CTx CR/PR: focal:10/3, whole-brain/ventricle:15/22, craniospinal:6/15/1(SD).	after CTx CR/PR: primary sites: 28–46 Gy/30.6–55 Gy, whole-brain: 18–36 Gy/23.4–30.6 Gy, spinal: 19.5–27 Gy/19.5–30.6 Gy.	2 cycles cisplatin and etoposide 56, carboplatin, etoposide, and cyclophosphamide 4, based etoposide regimens 12	unknown	RFS:5-year 97%, CSI, WBRT/WVRT, focal RT: 95%, 91%, and 62%; OS:5-year 87%, CSI, WBRT/WVRT, focal RT: 100%, 100%, and 83%	M/F:62/10	median (range):16(7–35)	Korea	median 87 months range(7-197)

Table 1 (continued)

Study Name/ AuthorYear	Publish Year	Sample Size (*N*)	Study Design	Tumor Extension (*N*)	Interventions (*N*)	RT Field (*N*)	Dose (boost) (Gy)	Chemothrapy (*N*)	Surgery (*N*)	Outcomes	Gender M/F (*N*)	Age (years)	Country/ Region	Follow-up (months)
Kanamori 2021	*2021*	66 *class I, II, and III: 41, class IV and V: 25*	multicenter retrospective study	class I, II, and III/class IV and V: pineal:14/6,neurohypophysis 6/3, basal ganglia 0/1,bifocal 18/15, pineal/basal ganglia 2/0,unknown 1/0; CSF cytology negative/positive:41/22	CSF positive 22; radiotherapy:22; biopsy/resection:15; chemotherapy:15	CSF positive 22 pts: whole-brain 6, whole-ventricle 5, craniospinal 11.	CSF positive 22 pts, CSI/non-CSI: primary site, median 44(24–52)/40(24–51)Gy, whole ventricle, median 24(23–44)/30(24–45)Gy, whole brain, median 24(23–32)/30(10–45)Gy, craniospinal, median 24(18–35)/0Gy.	platinum-based regimens similar in CSI/non-CSI	unknown	PFS, CSI and non-CSI groups (log-rank test, $p=0.37$)	CSI, M/F:7/3 non-CSI, M/F:7/4	CSI, median (range):12(7–40) non-CSI, median (range):16(9–28)	Janpan	CSI, median101 months(12–265) non-CSI, median 75 months(2-228)
Kang 2020	*2020*	34	single-center retrospective study	basal ganglia:34; localized:29; seeding:5	radiotherapy:34; biopsy/resection:14; chemotherapy:17	focal:14; whole ventricle:11; whole-brain:3; craniospinal:6	focal, tumor only, median 30(10–30)Gy, whole ventricle + PB, median 24.0(23.4–27) + 6(6–23)Gy, whole brain + PB, median 27.9(18–30) + 18(18-22.1)Gy, craniospinal + PB, median 22.5(19.8–30) + 22.6 (10.8–29.6)Gy.	6 to 10 cycles VBEP (vinblastine, bleomycin, cisplatin, etoposide); 6 to 10 cycles etoposide + carboplatin	craniotomy 9 pts, stereotactic biopsy 5 pts	DFS, 2-, 3-, and 5-year, 91.2%, 88.2%, 79.4%; OS, 2-, 3-, and 5-year, 97.1%, 94.1%, 82.4%; toxicity.	M/F:33/1	median (range):16(9–28)	Taipei	median 8.3 months(1.8–25.2)
Kawabata 2008	*2008*	39	single-center retrospective study	basal ganglia/other site:9/24; solitary/multifocal:33/6	radiotherapy:39; biopsy/resection:23; chemotherapy:16	focal:3; whole ventricle:17; whole-brain:6; craniospinal:13	primary site: median 46.8 Gy(19.8–60 Gy); whole-ventricle: median 23.4 Gy(20.4–27 Gy); whole-brain: median 35 Gy(25.2–51.2 Gy); craniospinal: median 24 Gy(10–40 Gy).	CARE (carboplatin and etoposide); VIP (ifosfamide, cisplatin, and etoposide)	biopsy 23 pts, no biopsy 13pts	OS,5- and 10-year, 97% and 90%; PFS,5- and 10-year,91% and 87%	M/F:29/10	median (range):15(7–27)	Janpan	median 94 months(18–300)
Koh 2022	*2022*	418	multicenter retrospective study	suprasellar:142;pineal:130; bifocal:69;basal ganglia:53; other (thalamus, etc.):24. M0/M+:334/84.	radiotherapy:418; biopsy/resection:318; chemotherapy:260	focal:58; whole ventricle:180; whole-brain:7; craniospinal:173	M0:median 21 Gy (CSI) and 23.4 Gy (WVI); M+:median 23.4 Gy (CSI) and 24.0 Gy (WVI); total tumor: median 36 Gy	carboplatin/etoposide and cyclophosphamide/etoposide 145pts, cisplatin/etoposide and cyclophosphamide/vincristine 21pts, carboplatin/etoposide and ifosfamide/etoposide 20pts, carboplatin/etoposide 20pts, cisplatin/etoposide 20pts, cisplatin/etoposide/bleomycin 13pts, 16pts other regimens,4 pts unknown.	biopsy 249pts, tumor removal (+ biopsy) 69pts, no resection 100pts	OS,5- and 10-year, 97.2% and 96.2%; RFS,5- and 10-year,89.9% and 86.9%	M/F:320/98	median (range):14.4(3.8–39.1)	Korea, Taiwan, Singapore, Japan	median 106.8 months

Table 1 (continued)

Study Name/ AuthorYear	Publish Year	Sample Size (*N*)	Study Design	Tumor Extension (*N*)	Interventions (*N*)	RT Field (*N*)	Dose (boost) (Gy)	Chemothrapy (*N*)	Surgery (*N*)	Outcomes	Gender M/F (*N*)	Age (years)	Country/ Region	Follow-up (months)
Lee 2019 KSPNO G051/G081	*2019*	91	multicenter prospective study	solitary:65; multiple/disseminated:26.	radiotherapy:91; biopsy/resection:91; chemotherapy:86	focal:4; whole ventricle:26; whole-brain:6; craniospinal:55	primary site: median 39.3 Gy(27–54)Gy; whole-ventricle: median 19.8 Gy(16.2–30.6)Gy; craniospinal: median 19.8 Gy(18–36) Gy.	4 cycles carboplatin/etoposide and cyclophosphamide/etoposide	biopsy 81pts, resection 10pts	OS:5-year and 7-year,98.8% and 98.8%; EFS:5-year and 7-year 96.6% and 93.8%; toxicity.	M/F:68/23	median (range):14(3–30)	Korea	median 67.9 months(6.6-119.3)
Lee 2021	*2021*	189	multicenter retrospective study	solitary: suprasellar 41/pineal 46/ BG/thalamus 29/others 3pts; bifocal: suprasellar and pineal 15/ suprasellar and other 5/ pineal and other 2/others 3pts; seeding (+):CSF cytology (+) 10/ multiple lesions in MRI (+) 22/ CSF cytology and MRI (+) 13pts.	radiotherapy:189; biopsy/resection:189; chemotherapy:139	RT/CTx + RT: focal:0/28; whole ventricle:0/56; whole-brain:5/4; craniospinal:45/51	RT: craniospinal, seeding+,median 24 Gy(20–30 Gy), seeding -,median 30 Gy(24–36 Gy); primary site:54 Gy(45–57 Gy). CTx + RT: extended-field, median 23 Gy(16–39 Gy); primary site: CR to CTx 45 Gy(25–50 Gy), non-CR to CTx 50 Gy(45–55 Gy).	66pts 2 cycles bleomycin, etoposide, and cisplatin or etoposide and cisplatin; 67pts 5 cycles cisplatin, etoposide, cyclophosphamide, and vincristine; 4pts"8-in-1"(solumedrol, vincristine, lomustine, procarbazine, hydroxyurea, cisplatin, cytosine arabinoside, and cyclophosphamide)	all were confirmed histologically.	OS: RT/CRT,10-year was 85.2%/92.8%; RFS: RT/CRT,79.5%/89.3%; toxicity.	M/F:151/38	median (range):15(4–47)	Korea	median 180 months(48–564)
Lee 2020 SMC-G13 trial	*2020*	41	single-center prospective study	suprasellar:12 pineal:12 bifocal (suprasellar + pineal):11 basal ganglia:6	radiotherapy:39; biopsy/resection:41; chemotherapy:41	whole ventricle:23; whole-brain:5; craniospinal:11	primary site:30.6 Gy(RBE); whole ventricle:18 Gy; whole-brain:18 Gy; craniospinal:18 Gy	4 cycles induction chemotherapy: CE regimen(carboplatin, etoposide), CyE regimen (cyclophosphamide, etoposide) alternated.	endoscopic biopsy:36, stereotactic biopsy:5	PFS:5-year,96.7%; OS:5-year,96.2%; toxicity.	M/F:31/10	median (range):15.9(7.5–34.1)	Korea	median 40.8 months(3.6–84)
Li 2021	*2021*	161	single-center retrospective study	basal ganglia:161	radiotherapy:161; biopsy/resection:30; chemotherapy:153	focal:35; whole-brain:109; craniospinal:17	primary site:40 Gy; whole-brain:30 Gy; craniospinal:30 Gy	2 cycles platinum-based induction chemotherapy (ifosfamide + etoposide + cisplatin), after RT additional 2 cycles CTx	biopsy:15, surgery:15, serum β-HCG elevation:131	DFS:5-year,92.0%, FR, WBRT, CSI was 74.3%, 97.2%, and 100%; OS:5-year,96.7%; toxicity.	M/F:150/11	median (range):12(5–41)	China	median 83 months(20–214)

Table 1 (continued)

Study Name/ AuthorYear	Publish Year	Sample Size (*N*)	Study Design	Tumor Extension (*N*)	Interventions (*N*)	RT Field (*N*)	Dose (boost) (Gy)	Chemothrapy (*N*)	Surgery (*N*)	Outcomes	Gender M/F (*N*)	Age (years)	Country/ Region	Follow-up (months)
Li 2020	*2020*	49	single-center retrospective study	bifocal: sellar/suprasellar + pineal gland:34; sellar/suprasellar + basal ganglia/thalamus:15	radiotherapy:49; biopsy/resection:13; chemotherapy:47	focal:3; whole-brain:34; craniospinal:12	primary site:40 Gy(2pts 45 Gy, 4pts 50.4 Gy); whole-brain:30 Gy; craniospinal:30 Gy	2 cycles platinum-based induction chemotherapy (ifosfamide + etoposide + cisplatin), after RT additional 2 cycles CTx	histology:13, serum/CSF β-HCG elevation:36	DFS:5-year,96.7%; OS:5-year, 97.3%; toxicity.	M/F:34/15	median (range):13(5–47)	China	median 52 months(10–134)
Lian 2018	*2018*	170	single-center retrospective study	localized: sellar and suprasellar 95, pineal 2,basal ganglia6; bifocal:47; disseminated:20	radiotherapy:170; biopsy/resection:56; chemotherapy:38	focal:2; whole ventricle:82; whole-brain:32; craniospinal:54	RT: primary site: median 45 Gy(29–52 Gy); whole-ventricle/whole-brain/CSI: median 25 Gy(19.8–36 Gy); CRT: primary site: median 36 Gy(30–40 Gy); whole-ventricle/whole-brain/CSI: median 20 Gy(17.8–25 Gy)	1–6 cycles platinum-based regimen (cisplatin + etoposide/ifosfamide + cisplatin + etoposide)	pathologically:56, clinically:114	RFS:5-and 10-year,91.9% and 78.1%; OS:5-and 10-year,94.5% and 91.3%; toxicity.	M/F:94/76	median (range):15(4–39)	China	median 64.5 months(4-260.5)
Lo 2020	*2020*	94	multi-center retrospective study	pineal:37,suprasellar:23,bifocal:14, multifocal:15,corpus callosum:2, thalamus:2,basal ganglia:1	radiotherapy:94; biopsy/resection:81; chemotherapy:32	CTx + RT/RT: focal:6/4; whole ventricle:15/7; whole-brain:1/5; craniospinal:10/46	RT: primary site: range(30.8–55 Gy); whole-ventricle: median 29.4 Gy(17.3–34.6 Gy); whole-brain: range(20.7–50 Gy); CSI: median 27.3 Gy(14.7–37.3 Gy) CRT: primary site: range(22.5–53.3 Gy); whole-ventricle: median 22.5 Gy(16.2–27.6 Gy); whole-brain: range(11.7–43.2 Gy); CSI: median 25.4 Gy(11.7–36.0 Gy)	cisplatin-based regimens:9, carboplatin-based regimens:21, carboplatin + etoposide/ cisplatin + cyclophosphamide:2	biopsy:43, subtotal resection:36, total resection:2	EFS:5-and 10-year,86.1%,84.3%; OS:5-and 10-year,93.1%,89.9%	M/F:82/12	median (range):20(15–39)	Canada	median 99.6 months
Nakamura 2006	*2006*	52	single-center retrospective study	pinel:10, suprasellar:11, pineal + suprasellar:5, basal ganglia:4	radiotherapy:30; biopsy/resection:26; chemotherapy:30	focal:7; extended local(whole ventricle):5; extended local + boost:16; whole-brain + boost:2	local 24 Gy; extended local 24 Gy; extended local 30 Gy + local boost 20 Gy; whole brain 30 Gy + local boost 20 Gy	carboplatin or cisplatin + etoposide:26; ifosphamide + cisplatin + etoposide:4	biopsy:22, patial resection:3, total resection:1, none:4	Recurrence Rate:13.3%; QoL.	M/F:21/9	median (range):17(4–53)	Japan	unknown
Nguyen 2006	*2006*	21	single-center retrospective study	pinel:6, suprasellar:8, multiple midline:7	radiotherapy:21; biopsy/resection:20; chemotherapy:12	focal:9; craniospinal:12	focal: median 30.6 Gy (range,30.0–44 Gy); craniospinal: primary site, median 50 Gy(range,44.8–58 Gy)/ CSI, median 24 Gy(range,20–36 Gy).	CTx + focal RT:9,CTx + CSI:3; carboplatin or cisplatin + etoposide:7, cisplatin + etoposide + cytoxan + vincristine:3, other cisplatin based regimens:2	biopsy:12, resection:8, none:1	PFS:5-year 100% for CSI,62% for focal RT; OS:10-year 83% for CSI,89% for focal RT	M/F:13/8	median (range):19(6–27)	USA	median 94 months(9.7–215)

Table 1 (continued)

Study Name/ AuthorYear	Publish Year	Sample Size (*N*)	Study Design	Tumor Extension (*N*)	Interventions (*N*)	RT Field (*N*)	Dose (boost) (Gy)	Chemothrapy (*N*)	Surgery (*N*)	Outcomes	Gender M/F (*N*)	Age (years)	Country/ Region	Follow-up (months)
Ogawa 2003	*2003*	126	multi-center retrospective study	pinel:51,neurohypophyseal:33, thalamus or basal ganglia:7, multifocal:21,disseminated:14	radiotherapy:126; biopsy/resection:50; chemotherapy:0	focal:6; whole ventricle:2; whole-brain:62; craniospinal:56	primary site: median 50 Gy(20–64 Gy); whole ventricle: range(40–42 Gy); whole-brain: median 30 Gy(19.5–44 Gy); craniospinal: median 30.4 Gy(7.2–37.2 Gy)	/	pathologically:50, clinically:76	OS:10-year,90%; CSS:10-year,95%; toxicity.	M/F:95/31	median (range):17(2–47)	Japan	median 122 months(13–263)
Lee 2023	2023	87	single-center retrospective study	solitary: suprasellar 16,pineal 39, basal ganglia/ thalamus:14,others 3; bifocal: suprasellar and pineal 2, suprasellar and other 7, pineal and other 3,others 3	radiotherapy:87; biopsy/resection:87; chemotherapy:87	focal:22; whole ventricle:65	primary site: focal/WV, median45Gy(36–54 Gy)/45Gy(23.4–55.8 Gy); whole ventricle: median19.8 Gy(14.4–36.0 Gy)	2 cycles bleomycin, etoposide and cisplatin or etoposide and carboplatin:36; 4 cycles etoposide, carboplatin, and cyclophosphamide:30; 4 cycles bleomycin, etoposide, cisplatin and cyclophosphamide:2; 2 cycles cisplatin, etoposide, ifosfamide:6; 5 cycles cisplatin, etoposide, cyclophosphamide and vincristine:7; 8-in-1(solumedrol, vincristine, lomustine, procarbazine, hydroxyurea, cisplatin, cytosine arabinoside and cyclophosphamide):4	stereotactic biopsy:26, endoscopic biopsy:44, open biopsy:9, surgery:8	RFS:10-year, 86.3%, OS:10-year, 90.9%, Dosimetric, Secondary malignancy	M/F:72/15	median (range):15(4–44)	Korea	median 93.6 months(5.88–270)
Schoenfeld 2006	*2006*	31	single-center retrospective study	pineal:23, suprasellar:5, pineal and suprasellar:3	radiotherapy:31; biopsy/resection:31; chemotherapy:2	focal:2; whole ventricle:1; craniospinal:28	primary site: median 49.5 Gy(range,30–51 Gy); whole ventricle: median 9 Gy(range,8–21 Gy); CSI, median 21 Gy(range,20–25 Gy).	carboplatin, etoposide, bleomycin or cisplatin, etoposide:2	tissue diagnosis:31	OS:5- and 10-year,93% and 88%, RFS:5- and 10-year,94% and 94%, toxicity.	M/F:27/4	median (range):18(10–36)	USA	median 84 months(21.6–246)

Table 1 (continued)

Study Name/ AuthorYear	Publish Year	Sample Size (N)	Study Design	Tumor Extension (N)	Interventions (N)	RT Field (N)	Dose (boost) (Gy)	Chemothrapy (N)	Surgery (N)	Outcomes	Gender M/F (N)	Age (years)	Country/ Region	Follow-up (months)
Shibamoto 1988	*1988*	70	single-center retrospective study	pineal(P):33, supra- or intrasellar(S):26, P + S:6, basal ganglia/thalamus:5	radiotherapy:70; biopsy/resection:30; chemotherapy: unknown	focal:34; whole ventricle + spine:6; whole-brain:4; craniospinal:22; others:4	primary site:50–55 Gy; whole-brain:30 Gy; craniospinal: median 24 Gy	unknown	biopsy:19, patial resection:6, total resection:3, other:2, cytology:12,clinicaly:28	OS:5- and 10-year,86% and 79%, RFS, unknown, toxicity.	M/F:57/13	median (range):15(6–44)	Japan	unkown
Shikama 2005	*2005*	180	multi-center retrospective study	solitary: pineal 60,suprasellar 53, basal ganglia 16; multiple or disseminated:51	radiotherapy:180; biopsy/resection:88; chemotherapy:55	focal:14; whole ventricle/ brain:100; craniospinal:66	primary site: median 50 Gy(24–64 Gy); whole-brain/ventricle: median 30 Gy(12–54 Gy); craniospinal: median 30 Gy(7.2–37.5 Gy)	1 to 5 cycles etoposide plus cisplatin or carboplatin 40, cisplatin, bleomycin, nitrosourea and other agents 15, intrathecal methotrexate 3.	pathologic 88, clinical 92	OS:8-year,91% ; EFS:8-year,89% ; 8-year recurrence rates at primary site, intracranial, and spinal were 1%, 6%, and 6%; toxicity.	M/F:133/47	median (range):16(1–47)	Japan	median 89 months(3-297)
Shirato 1997	*1997*	51	single-center retrospective study	pineal:16,suprasellar:11, pineal + suprasellar:11, basal ganglia:5,thalamus:4, third ventricle:1, third ventricle + suprasellar:3	radiotherapy:51; biopsy/resection:18; chemotherapy:18	focal:5; whole ventricle:21; whole-brain:9; craniospinal:16	primary site: median 47.1 Gy(30–60 Gy); whole-brain/ventricle: median 30 Gy(20–40 Gy); craniospinal: median 30 Gy(20–39 Gy)	5 cycles ifosfamide, cisplatin, etoposide	pathologic 18, clinical 33	OS:10-year,92%, CSS:10-year, PVG and PUVG was 100 and 96%, toxicity.	M/F:42/9	median (range):19(9–32),PVG; median (range):15(5–28),PUVG	Japan	median 108 months(0.71–204)
Singh 2015	*2015*	28	multi-center retrospective study	bifocal:28	radiotherapy:28; biopsy/resection:13; chemotherapy:26	focal:10; whole ventricle:14; craniospinal:4	primary site: median 38 Gy; whole-ventricle: median 24 Gy(30.6–40 Gy); craniospinal: unknown	adjuvant chemoterapy	surgery 13	Recurrence Rate	M/F:24/4	median (range):14.1(6.7–21.8)	Canada, USA	WVRT + boost median 78 months WVRT median 50.4 months
Takami 2021	*2021*	35	single-center retrospective study	neurohypophyseal 20, bifocal, neurohypophyseal + pineal 15	radiotherapy:33; biopsy/resection:32; chemotherapy:25	focal:12; whole ventricle:3; craniospinal:15	ACNS0232 study protocol	ACNS0232 study protocol	endoscopic surgery 9, stereotactic biopsy 5, open craniotomy 15, unknown surgery 3	PFS, OS, toxicity; whole-brain or whole-ventricle RT significantly improved PFS and OS vs. local RT.	M/F:26/9	median (range):18(0.25-49)	USA	unknown

Table 1 (continued)

Study Name/ AuthorYear	Publish Year	Sample Size (*N*)	Study Design	Tumor Extension (*N*)	Interventions (*N*)	RT Field (*N*)	Dose (boost) (Gy)	Chemothrapy (*N*)	Surgery (*N*)	Outcomes	Gender M/F (*N*)	Age (years)	Country/ Region	Follow-up (months)
Takano 2015	*2015*	38	single-center retrospective study	pineal 17, neurohypophysial 11, multiple 6,basal ganglia 2, others 2	radiotherapy:38; biopsy/resection:32; chemotherapy:32	focal(CTx):16; whole ventricle(CTx):17; whole-brain(RT alone):5	Group A: whole-brain 30.6 Gy + boost 19.8 Gy; Group B: CTx + local 30.6 Gy or extended local (24–30.6 Gy); Group C: CTx + whole-ventricle 30.6 Gy + local boost 19.8 Gy	Group B: cisplatin + etoposide 11, bleomycin + vincristine + cisplatin 3, ifosfamide + cisplatin + etoposide 1 Group C:3 cycles cisplatin or carboplatin + etoposide 17	pathological: Group A/B/C:1/14/17	PFS:5-and 10-year,92.1% and 73.9%; OS:5-and 10-year,100% and 95.5%; toxicity.	M/F:29/9	median (range):16.5(7–38)	Japan	median 128.3 months(60–384)
Tsurubuchi 2022	*2022*	43	single-center retrospective study	pineal 26, sellar 18, lateral ventricle 8, cerebral hemisphere 3, basal ganglia 2, others 4	radiotherapy:43; biopsy/resection:43; chemotherapy:41	focal:9; RT including WV:34	primary site: range,39.4–50.4 Gy; whole ventricle: range,23.4–30.6 Gy; CSI,23.4 Gy	cisplatin and etoposide, vincristine, cisplatin, and/or bleomycin, ifosfamide, cisplatin, and etoposide, carboplatin and etoposide	endoscopic biopsy 17, craniotomy or laminectomy 17, transsphenoidal surgery 7, stereotactic biopsy 4	PFS and OS, 5-year, 88% and 100%	M/F:33/10	no/delayed/early recurrence: median (range):14(7–38)/ median (range):23.5(8–38)/ median (range):15.5(14–21)	Japan	no/delayed/early recurrence: median 143.5 months(60–380) median 207.5 months(88–222) median 207.5 months(88–222)
Weksberg 2012	*2012*	20	single-center retrospective study	bifocal, pineal + suprasellar:20	radiotherapy:20; biopsy/resection:13; chemotherapy:7	focal:1; whole ventricle:5; whole-brain:3; craniospinal:11	primary site: median 50 Gy(19.5–58 Gy)	ifosfamide, cisplatin, and etoposide 2, carboplatin and etoposide 4, cisplatin and etoposide 1	biopsy 13	PFS, 5-year, 100%	M/F:19/1	median (range):19(8–47)	Japan	median 99.5 months(33–256)
Cheng 2014	*2014*	25	single-center retrospective study	suprasellar 9,bifocal 8, pineal 6,basal ganglia 2	radiotherapy:25; biopsy/resection: unknown; chemotherapy:24	focal:4; whole ventricle:15; whole-brain:3; craniospinal:3	focal(40 Gy); whole-ventricular(23.4–24 Gy) + boost(16 Gy); whole-brain(23.4 Gy); CSI unknown dose	carboplatin-based	unknown	PFS, 5-year, 96%; OS, 5-year, 100%; Education Status.	M/F:14/11	median (range):12.9(6–17)	Canada	median 61 months(1-144)

CTx: chemotherapy; RT: radiotherapy; CRT: chemo-radiotherapy; CSI: craniospinal irradiation; WBRT: whole-brain RT; WVRT: whole-ventricle RT; OS: overall survival; PFS/EFS/DFS/RFS: progression/event/disease/relapse free survival; QoL: quality of life; pts: patients; CSF: cerebrospinal fluid

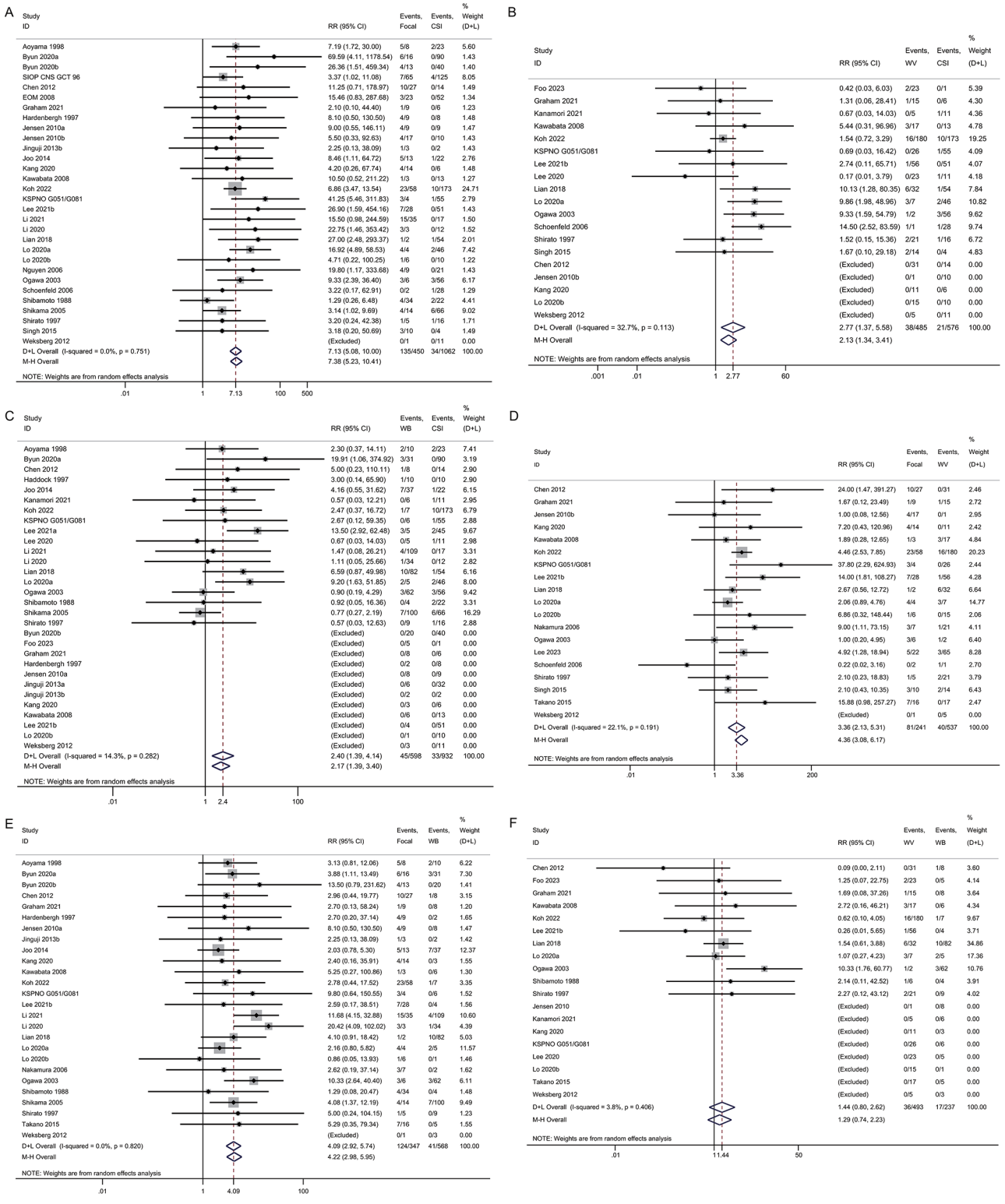

Fig. 2 Results of meta-analyses regarding recurrence rate of intracranial germinoma in full-set. **A**: Meta-analysis of focal radiotherapy (RT) vs. craniospinal irradiation (CSI); **B**: Meta-analysis of whole-ventricle radiotherapy (WVRT) vs. CSI; **C**: Meta-analysis of whole-brain radiotherapy (WBRT) vs. CSI; **D**: Meta-analysis of focal RT vs. WVRT; **E**: Meta-analysis of focal RT vs. WBRT; **F**: Meta-analysis of WVRT vs. WBRT

Table 2 Meta-analyses of recurrence rate and mortality in full-set

Comparisons	Statistic Model	Relapse				Death			
		Events/Total(*N*)	RR, 95% CI	*P* value	I^2/τ^2	Events/Total(*N*)	RR, 95% CI	*P* value	I^2/τ^2
Focal RT vs. CSI	D+L pooled RR	135/450 vs. 34/1062	7.128(5.083,9.995)	< 0.001	0%/0.0000	37/380 vs. 22/824	3.134(1.804,5.446)	< 0.001	2.3%/0.0329
	M-H pooled RR		7.381(5.234,10.410)				2.932(1.789,4.804)		
WVRT vs. CSI	D+L pooled RR	38/485 vs. 21/576	2.771(1.375,5.584)	0.004	32.7%/0.5128	10/401 vs. 16/437	1.311(0.425,4.047)	0.638	51.6%/1.4156
	M-H pooled RR		2.134(1.337,3.406)				0.820(0.434,1.547)		
WBRT vs. CSI	D+L pooled RR	45/598 vs. 33/932	2.397(1.388,4.140)	0.002	14.3%/0.1927	15/417 vs. 17/629	2.103(0.980,4.514)	0.056	0.0%/0.0000
	M-H pooled RR		2.175(1.390,3.404)				1.817(0.889,3.714)		
Focal RT vs. WVRT	D+L pooled RR	81/241 vs. 40/537	3.361(2.126,5.312)	< 0.001	22.1%/0.1866	21/239 vs. 11/453	2.559(1.263,5.185)	0.009	4.1%/0.0666
	M-H pooled RR		4.362(3.082,6.174)				2.800(1.556,5.037)		
Focal RT vs. WBRT	D+L pooled RR	124/347 vs. 41/568	4.094(2.923,5.735)	< 0.001	0.0%/0.0000	35/300 vs. 15/408	2.635(1.504,4.614)	0.001	0.0%/0.0000
	M-H pooled RR		4.216(2.985,5.955)				2.748(1.606,4.703)		
WVRT vs. WBRT	D+L pooled RR	36/493 vs. 17/237	1.444(0.796,2.619)	0.227	3.8%/0.0418	9/424 vs. 3/91	0.533(0.184,1.541)	0.245	0.0%/0.0000
	M-H pooled RR		1.288(0.743,2.233)				0.567(0.217,1.482)		

CSI: craniospinal irradiation; WBRT: whole-brain radiotherapy; WVRT: whole-ventricle radiotherapy; RR: risk ratio

and fixed effect model were both employed, and more detailed meta-analyses results were shown in Table 2.

Recurrence in RT alone subset

We systematically evaluate recurrence in RT alone subset. Four studies with 236 IG patients assessed the relapse rate of focal RT vs. CSI. Pooled RR manifested that focal field RT were with higher recurrence in comparison with CSI [RR=14.469, 95% CI (6.293, 33.265), P=0.000]. Only two studies with 111 IG patients were included in this meta-analysis to calculate relapse rate of WVRT vs. CSI. Pooled RR indicated WVRT were with higher recurrence compared with CSI [RR=9.618, 95% CI (2.932, 31.552), P=0.000]. Six studies with 395 IG patients assessed the relapse rate of WBRT vs. CSI. Pooled RR indicated that WBRT were with higher recurrence in comparison with CSI [RR=5.989, 95% CI (1.347, 26.625), P=0.019, I^2=62.1%]. Only two studies with 19 IG patients were included in this meta-analysis to calculate relapse rate of focal RT vs. WVRT. Pooled RR showed that no significant difference between focal RT and WVRT [RR=1.761, 95% CI (0.838, 3.701), P=0.135]. Four studies with 141 IG patients were included in meta-analysis to evaluate recurrence rate of focal RT vs. WBRT. Pooled RR also indicated focal field RT were with higher recurrence compared with WBRT [RR=4.102, 95% CI (1.945, 8.650), P=0.000]. Only two studies with 76 IG patients were included in this meta-analysis to evaluate relapse rate of WVRT vs. WBRT. Pooled RR manifested no significant difference between WVRT and WBRT [RR=3.117, 95% CI (0.303, 32.023), P=0.339]. In these meta-analyses, no obvious heterogeneity was found (except for WBRT vs. CSI, I^2=62.1%, τ^2=1.3962), the random and fixed effect

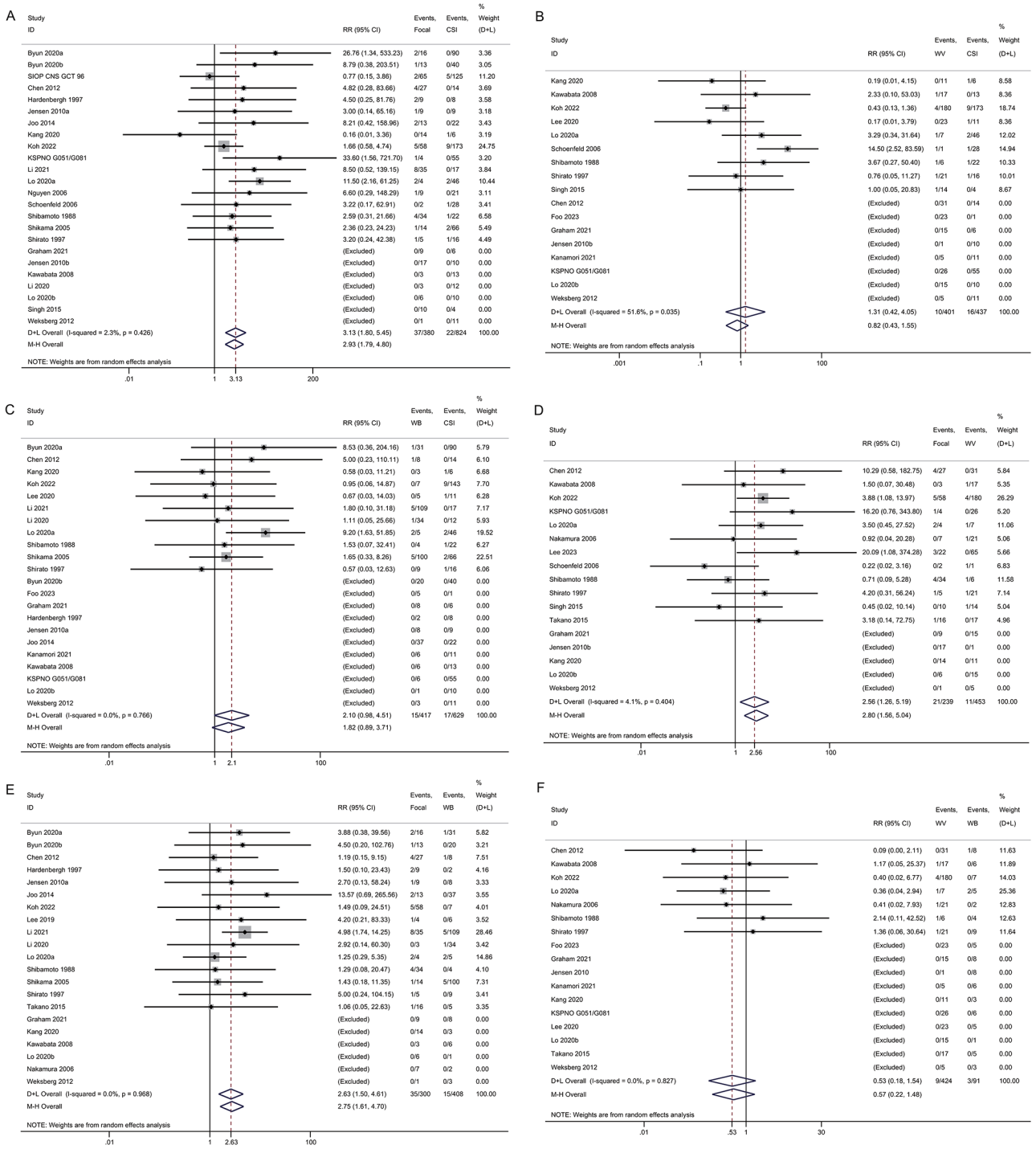

Fig. 3 Results of meta-analyses regarding mortality of intracranial germinoma in full-set. **A**: Meta-analysis of focal radiotherapy (RT) vs. craniospinal irradiation (CSI); **B**: Meta-analysis of whole-ventricle radiotherapy (WVRT) vs. CSI; **C**: Meta-analysis of whole-brain radiotherapy (WBRT) vs. CSI; **D**: Meta-analysis of focal RT vs. WVRT; **E**: Meta-analysis of focal RT vs. WBRT; **F**: Meta-analysis of WVRT vs. WBRT

model were both employed, and more detailed meta-analyses results were shown in Table 3.

Mortality in RT alone subset

Three studies with 174 patients assessed mortality rate of focal RT vs. CSI in RT alone subset. Pooled RR indicated that focal RT was with higher mortality compared with CSI [RR=10.589, 95% CI (2.831, 39.603), *P*=0.000]. Only one study with 53 IG patients evaluated mortality of WVRT vs. CSI, indicated that no significant difference between WVRT and CSI [RR=3.286, 95% CI (0.341, 31.643), *P*=0.303]. Three studies with 189 IG patients assessed mortality of WBRT vs. CSI. Pooled RR indicated that WBRT was with higher mortality than CSI [RR=9.043, 95% CI (1.981, 41.283), *P*=0.004]. Only one study with 11 patients evaluated mortality of focal RT vs. WVRT, indicated that no difference between focal RT and WVRT [RR=3.500, 95% CI (0.445, 27.524), *P*=0.234]. Three studies with 73 IG patients were included in the meta-analysis to evaluated mortality of focal RT vs. WBRT. Pooled RR indicated that no difference between focal RT and WBRT [RR=1.830, 95% CI (0.583, 5.741), *P*=0.301]. Only one study with 12 patients evaluated mortality of WVRT vs. WBRT, manifested no significant difference between WVRT and WBRT group [RR=0.357, 95% CI (0.043, 2.941), *P*=0.338]. In these meta-analyses, no obvious heterogeneity was found, both random and fixed effect model were employed, and more detailed pooled results were shown in Table 3.

Table 3 Meta-analyses of recurrence rate and mortality in RT alone subset

Comparisons	Statistic Model	Relapse				Death			
		Events/Total(*N*)	RR, 95% CI	*P* value	I^2/τ^2	Events/Total(*N*)	RR, 95% CI	*P* value	I^2/τ^2
Focal RT vs. CSI	D+L pooled RR	17/35 vs. 5/201	14.469(6.293,33.265)	< 0.001	0.0%/0.0000	5/29 vs. 2/145	10.589(2.831,39.603)	<0.001	0.0%/0.0000
	M-H pooled RR		16.876(6.658,42.779)				9.610(2.532,36.481)		
WVRT vs. CSI	D+L pooled RR	4/9 vs. 5/102	9.618(2.932,31.552)	<0.001	0.0%/0.0000	1/7 vs. 2/46	3.286(0.341,31.643)	0.303	/
	M-H pooled RR		9.710(2.757,34.197)				3.286(0.341,31.643)		
WBRT vs. CSI	D+L pooled RR	11/117 vs. 7/278	5.989(1.347,26.625)	0.019	62.1%/1.3962	3/44 vs. 2/145	9.043(1.981,41.283)	0.004	0.0%/0.0000
	M-H pooled RR		4.051(1.871,8.770)				8.933(1.757,45.417)		
Focal RT vs. WVRT	D+L pooled RR	7/10 vs. 4/9	1.761(0.838,3.701)	0.135	0.0%/0.0000	2/4 vs. 1/7	3.500(0.445,27.524)	0.234	/
	M-H pooled RR		1.679(0.800,3.526)				3.500(0.445,27.524)		
Focal RT vs. WBRT	D+L pooled RR	17/35 vs. 8/106	4.102(1.945,8.650)	<0.001	17.5%/0.1052	5/29 vs. 3/44	1.830(0.583,5.741)	0.301	0.0%/0.0000
	M-H pooled RR		4.200(2.092,8.431)				2.104(0.662,6.693)		
WVRT vs. WBRT	D+L pooled RR	4/9 vs. 5/67	3.117(0.303,32.023)	0.339	76.9%/2.1810	1/7 vs. 2/5	0.357(0.043,2.941)	0.338	/
	M-H pooled RR		1.760(0.621,4.987)				0.357(0.043,2.941)		

CSI: craniospinal irradiation; WBRT: whole-brain radiotherapy; WVRT: whole-ventricle radiotherapy; RR: risk ratio

Table 4 Meta-analyses of recurrence rate and mortality in CTx plus RT subset

Comparisons	Statistic Model	Relapse				Death			
		Events/Total(*N*)	RR,95% CI	*P* value	I^2/τ^2	Events/Total(*N*)	RR,95% CI	*P* value	I^2/τ^2
Focal RT vs. CSI	D+L pooled RR	41/119 vs. 1/201	12.368(5.046,30.314)	<0.001	0.0%/0.0000	10/88 vs. 0/148	13.270(2.361,74.582)	0.003	0.0%/0.0000
	M-H pooled RR		11.825(4.802,29.119)				10.623(1.642,68.725)		
WVRT vs. CSI	D+L pooled RR	3/135 vs. 2/141	0.871(0.187,4.053)	0.861	0.0%/0.0000	1/79 vs. 1/90	0.419(0.047,3.697)	0.433	0.0%/0.0000
	M-H pooled RR		0.868(0.226,3.333)				0.394(0.054,2.857)		
WBRT vs. CSI	D+L pooled RR	5/181 vs. 2/198	1.306(0.286,5.961)	0.730	0.0%/0.0000	6/175 vs. 1/145	1.127(0.199,6.384)	0.893	0.0%/0.0000
	M-H pooled RR		1.244(0.278,5.573)				1.169(0.212,6.445)		
Focal RT vs. WVRT	D+L pooled RR	37/119 vs. 12/249	4.643(2.546,8.468)	<0.001	0.0%/0.0000	5/82 vs. 2/159	3.517(0.795,15.554)	0.097	15.3%/0.4391
	M-H pooled RR		5.759(3.214,10.317)				3.561(1.235,10.265)		
Focal RT vs. WBRT	D+L pooled RR	37/99 vs. 5/178	8.183(4.111,16.287)	<0.001	0.0%/0.0000	10/68 vs. 6/172	4.639(1.882,11.431)	0.001	0.0%/0.0000
	M-H pooled RR		7.426(3.844,14.345)				4.658(1.878,11.553)		
WVRT vs. WBRT	D+L pooled RR	2/141 vs. 0/18	0.331(0.039,2.786)	0.309	0.0%/0.0000	1/85 vs. 0/14	0.409(0.021,7.931)	0.555	/
	M-H pooled RR		0.335(0.040,2.792)				0.409(0.021,7.931)		

CSI: craniospinal irradiation; WBRT: whole-brain radiotherapy; WVRT: whole-ventricle radiotherapy; RR: risk ratio

Recurrence in CTx plus RT subset

We systematically evaluate recurrence in CTx + RT subset. Nine studies with 320 IG patients assessed the recurrence rate of focal RT vs. CSI. Pooled RR indicated that focal RT were with higher recurrence compared with CSI [RR=12.368, 95% CI (5.046, 30.314), P=0.000]. Six studies with 276 IG patients were included to this meta-analysis to calculate relapse of WVRT vs. CSI. Pooled RR indicated that no significance between WVRT and CSI [RR=0.871, 95% CI (0.187, 4.053), P=0.861]. Eight studies with 379 IG patients assessed the relapse rate of WBRT vs. CSI. Pooled RR manifested that no significant difference between WBRT and CSI [RR=1.306, 95% CI (0.286, 5.961), P=0.730]. Nine studies with 368 IG patients were included in the meta-analysis to calculate recurrence rate of focal RT vs. WVRT. Pooled RR indicated that focal RT were with higher recurrence compared with WVRT [RR=4.643, 95% CI (2.546, 8.468), P=0.000]. Eight studies with 277 IG patients were included in meta-analysis to evaluate relapse rate of focal RT vs. WBRT. Pooled RR also indicated focal RT were with higher recurrence compared with WBRT [RR=8.183, 95% CI (4.111, 16.287), P=0.000]. Five studies with 159 IG patients were included into meta-analysis to evaluate relapse rate of WVRT vs. WBRT. Pooled RR showed that there was no significant difference between WVRT and WBRT [RR=0.331, 95% CI (0.039, 2.786), P=0.309]. In these meta-analyses, no obvious heterogeneity was found, the random and fixed effect model were both employed, and more detailed pooled results were shown in Table 4.

Mortality in CTx plus RT subset

Seven studies with 236 IG patients assessed the mortality of focal RT vs. CSI in CTx + RT subset. Pooled RR indicated that focal RT was with higher mortality compared with CSI [RR=13.270, 95% CI (2.361, 74.582), P=0.003]. Five studies with 169 patients evaluated mortality of WVRT vs. CSI. Pooled RR showed that no significant difference between WVRT and CSI [RR=0.419, 95% CI (0.047, 3.697), P=0.433]. Six studies with 320 IG patients assessed the mortality of WBRT vs. CSI. Pooled RR also indicated no significant difference between WBRT and CSI [RR=1.127, 95% CI (0.199, 6.384), P=0.893]. Seven studies with 241 patients evaluated mortality of focal RT vs. WVRT. Pooled RR manifested there was borderline significance between focal RT and WVRT [RR=3.517, 95% CI (0.795, 15.554), P=0.097]. Six studies with 240 IG patients were included in the meta-analysis to evaluated mortality of focal RT vs. WBRT. Pooled RR indicated focal RT was with higher mortality in comparison with WBRT [RR=4.639, 95% CI (1.882, 11.431), P=0.001]. Four studies with 99 patients evaluated mortality of WVRT vs. WBRT. RR manifested no significant difference between WVRT and WBRT arm [RR=0.409, 95% CI (0.021, 7.931), P=0.555]. In these meta-analyses, no obvious heterogeneity was found, the random and fixed effect model were both employed, and more detailed pooled results were shown in Table 4.

Toxicity

Twenty-four studies reported treatment-related acute and/or late toxicity. Most studies only qualitatively described toxicity, and it is difficult to quantitatively pool the differences in toxicity rates between different intervention approaches. To sum up, combination chemotherapy increased acute toxic effects, such as acute hematologic toxicities, nausea and vomiting; while expanded RT fields and/or RT doses increased late toxicity, such as neurocognitive dysfunctions, hormone deficiency, school activity, and secondary malignancy. More details were summarized in Supplementary Table 2.

Discussion

Main findings

This study has following main findings: Firstly, meta-analyses manifested focal RT were with higher recurrence and mortality compared with CSI, WBRT or WVRT, while CSI had the lowest recurrence rate in full-set; WBRT and WVRT were also with higher recurrence compared with CSI; no significant difference regarding to mortality between WVRT and CSI; no significant difference in recurrence and mortality rate between WVRT and WBRT. Secondly, Meta-analyses demonstrated focal RT/WVRT/WBRT were with higher recurrence rate compared with CSI in RT alone subset; either focal RT vs. WVRT or WVRT vs. WBRT, no significant difference in recurrence. Meta-analyses indicated focal RT were with higher recurrence compared with CSI, WBRT or WVRT in CTx+RT subset; no significant difference regarding to recurrence in any one of comparisons (WVRT vs. CSI, WBRT vs. CSI, WVRT vs. WBRT). Thirdly, combination chemotherapy increased acute toxic effects, and expanded RT fields and/or higher doses increased acute and late toxicity.

Strength of evidence

In this systematic review and meta-analysis, those treated with focal RT had an excessively higher recurrence rate, while CSI had the lowest recurrence rate. Focal field radiotherapy has a higher spinal failure rate than CSI [9, 15–17, 22, 24]. This has also been confirmed by multiple previously published studies [17, 22, 23, 25, 26]. Our findings together with those of previous studies suggest focal field RT is inappropriate for localized intracranial germinoma, regardless of whether combined with chemotherapy.

CSI has the lowest recurrence rate, so is this strategy still necessary? According to a study performed by Schoenfeld et al., RT alone with low-dose prophylactic CSI cures almost all patients with germinoma, and complications are rare [41]. In other studies, researchers thought that spinal irradiation might be omitted. A multicenter study showed that spinal irradiation did not contribute to favorable event-free survival in patients with IG [43]. The study by Kanamori et al. also suggested that CSI is unnecessary for germinoma patients with positive CSF cytology without spinal lesions on MR imaging [27]. Rather than omit CSI, some studies have used a milder approach that can be treated with reduced-dose CSI alone for localized germinoma, and reduced-dose CSI alone is effective in metastatic IG disease [7]. Hardenbergh et al. also suggested that CSI may be indicated for patients with multiple or spine seeding [23]. In a word, CSI is not necessary for localized intracranial germinoma, considering the efficacy, toxicity, number and spread of lesions, reduced-dose CSI alone with or without CTx is effective in multiple or metastatic IG.

This meta-analysis demonstrated that WVRT or WBRT were with higher recurrence rate compared with CSI in RT alone, but no significant difference between WVRT and WBRT; also no significant difference regarding to recurrence in any one of comparisons (WVRT vs. CSI, WBRT vs. CSI, WVRT vs. WBRT) in CTx + RT. Joo et al. reported that WBRT or WVRT could be applied to patients who show a complete response to chemotherapy [26]. Reduced field of radiation needs to encompass the whole-ventricular for bifocal germinoma [45]. RT including whole-ventricle system decreased delayed craniospinal relapses including dissemination, local, and

distant recurrences even ≥ 5 years after CR in patients with intracranial germinoma [48]. WVRT or WBRT + primary boost is a sufficient irradiation field for localized IG, while patients with bifocal disease should undergo CSI, especially when treated with RT alone. The results of chemotherapy followed by reduced-dose RT are comparable to those of RT alone [35]. Based on the results of our study and the discussion above, whole-ventricular or whole-brain radiotherapy should be the preferred modality for localized lesions.

Some studies support the addition of chemotherapy to radiotherapy for intracranial germinoma. Chemotherapy followed by whole-ventricle radiotherapy, with or without local boost, and with use of neuro-endoscopy results in good disease-control without late complications in germinoma patients [47]. Currently used upfront chemotherapy followed by reduced-dose/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 [30]. A previous meta-analysis showed CRT strategy has a higher overall survival and disease-free survival at 3 years than RT, but the advantage of survival rates for CRT is eliminated or even reversed at 5 years in the postoperative period [50]. All above results suggest that the addition of chemotherapy may reduce RT volume and/or doses. However, some studies have come to a different conclusion. The additional benefit of CTx in the treatment of IG seems minimal, and RT-only approach with reduced target volume and dose seems reasonable [16]. Focal RT with or without CTx were associated with inferior control of IG and a higher incidence of CTx-related toxicities. Adjustment of the radiation volume to the whole ventricular system without CTx is sufficient for treatment of non-disseminated IG, even with lower primary RT doses (< 36 Gy) [17]. On the basis of our findings and those of previously studies, we conclude that whole-ventricle or whole-brain radiotherapy is adequate, regardless of whether combined with chemotherapy.

This meta-analysis together with previous studies showed that whole-ventricle irradiation with or without boost at total dose of 36–40 Gy for primary lesion and 23.4 Gy for whole-ventricle system, using precise radiation therapy of treatment planning, is appropriate as a standard treatment for most localized intracranial germinoma. Adjustment of the radiation volume to the whole-ventricular system without CTx is sufficient for treatment of non-disseminated IG, even with lower RT doses (< 36 Gy) [17]. The radiation dose can also be further reduced if chemotherapy is combined. A study showed that upfront chemotherapy could be beneficial for the patients with complete response to minimize the RT dose down to 30 Gy [31]. In another study by Foo et al., excellent 5-year PFS and OS were achieved with chemotherapy followed by radiotherapy of 23.4 Gy delivered without primary tumor boost [20]. Due to the heterogeneity of radiation doses reported by different included studies, it was not feasible to quantitatively pooled results, recommendations for radiation dose are summarized as follows: (1) for localized intracranial germinoma, 20–24 Gy for whole-ventricle system and total dose up to 36–40 Gy for primary sites is required; (2) for multiple or metastatic IG, CSI at dose of 19.8–23.4 Gy and total dose up to 39.6–45 Gy for primary lesions is effective.

This systematic review indicated that most of the surviving patients are living an active, useful life, although some patients have hypothalamic-pituitary dysfunction, visual disturbance, or other neurological deficits. All of the symptoms existed from the beginning and may not be the sequalae of surgery and radiotherapy. QoL of surviving patients did not appear to differ significantly between the locally-treated and the CSI groups. Karnofsky performance status, educational achievement, and the ability to work were generally good, particularly in patients with tumors that did not involve the neurohypophyseal region. Because most complications, such as hormonal deficiency and neurocognitive dysfunction, were documented before RT and newly diagnosed complications after RT were infrequent, the treatment toxicity faced by germinoma patients appears to be less than anticipated [39]. Although radiotherapy rarely caused late adverse effects in patients with adolescent- or adult-onset, in some childhood-onset lesions, the radiation seems to carry the risk of neurocognitive dysfunctions, which are attributable to late adverse effects [25]. Pretreatment biochemical abnormalities may indicate higher risk of post-treatment pituitary insufficiency, and all patients should receive careful endocrine follow-up [46].

Limitations

There are several limitations of this meta-analysis. Firstly, all included studies were non-randomized, and most of included studies were retrospective, and most of the studies did not adjust for confounding factors, which weaken the level of evidence based on the results drawn. Secondly, due to the lack of stratification by local vs. disseminated disease in the most included studies, the meta-analysis included patients with both localized and disseminated disease, thus, it is almost impossible to conduct a meta-analysis, and the results may therefore exaggerate the value of CSI in localized disease. It is hoped that prospective controlled studies in the future need to stratified intervention according to the presence or absence of cerebrospinal fluid dissemination. Thirdly, though the I^2 in our study was low and acceptable, showing no concerned statistical heterogeneity, it might result from the high and similar cure rate of among different groups. In fact, the choice of treatment strategy varied

among different studies, including the radiation equipment, technique and dose as well as the chemotherapy regimen, increased the heterogeneity of the pooled results. Fourthly, since the toxicity and QoL of different treatment strategies were reported diversely, it was hard to quantify and drew a pooled result. Thus, we could not quantitatively compare the adverse effects of different treatment modalities. Fifthly, the arms of some studies overlapped in different comparisons of meta-analyses, and this situation could still lead to Type I error inflation. Therefore, limitations caused by multiple comparisons should be carefully considered when interpreting the results. Nevertheless, our study represents the highest level of evidence available regarding the efficacy and safety of different treatment modalities for intracranial germinoma, and ultimately facilitates clinical decision making.

Conclusion

In summary, long-term survival of IG patients treated with radiotherapy is excellent. Based on the available evidence and our findings, focal field RT is not recommended due to its highest recurrence rate regardless of whether combined with CTx for intracranial germinoma. Although CSI with or without CTx is associated with better local control than other reduced field RT, considering the potential toxicity and the pattern of relapse, whole ventricles irradiation field is more reasonable for localized or nonmetastatic intracranial germinoma. Reduced-dose CSI with or without CTx is effective in metastatic or disseminated germinoma.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-024-13323-1.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Acknowledgements
None.

Author contributions
Study concept and design: Y.M., Y.W., ZR.Z., EM.W.; Data collection: ZR.Z., JB.L., Q.Y., X.L., XW.Z., L.Z; Data analysis and interpretation: ZR.Z., JB.L., Q.Y., Y.M., Y.W., L.C.; Statistics: ZR.Z., JB.L., Q.Y., L.Z.; Manuscript drafting: ZR.Z., JB.L., Q.Y., X.L. XW.Z.; Manuscript revising: Y.M., Y.W., ZR.Z., EM.W. All authors reviewed the manuscript.

Funding
This work was supported by the National Natural Science Foundation of China (grant 82003231 to Dr. ZRZ).

Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Radiation Oncology Center, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai 200040, China
[2]National Center for Neurological Disorders, Shanghai 200052, China
[3]Department of Neurosurgery, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai 200040, China
[4]Department of Orthopedics, Advanced Medical Research Institute, Cheeloo College of Medicine, Qilu Hospital of Shandong University, Shandong University Centre for Orthopedics, Shandong University, Jinan, Shandong 250012, China
[5]Department of Oncology, Jing'an District Central Hospital, Fudan University, Shanghai 200040, China
[6]Nursing Department, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai 200040, China
[7]Department of Radiation Oncology, Taizhou Cancer Hospital, Wenling, Taizhou 317500, Zhejiang, China
[8]Department of Neurosurgery, CyberKnife Center, Huashan Hospital, Fudan University, Shanghai 200040, China
[9]Department of Neurosurgery, Huashan Hospital, Shanghai Medical College, Fudan University, No. 12 Urumchi Middle Road, Shanghai 200040, China
[10]National Center for Neurological Disorders, No. 958 Jin Guang Road, Shanghai 200052, China
[11]Radiation Oncology Center, Huashan Hospital, Shanghai Medical College, Fudan University, No. 12 Urumchi Middle Road, Shanghai 200040, China

Received: 4 June 2024 / Accepted: 10 December 2024
Published online: 07 January 2025

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