Review Article

Intracranial germ cell tumors in pediatric and adolescent patients in China: systematic review and meta-analysis

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Background: Intracranial germ cell tumors (IGCTs) are rare neoplasms occurring predominantly in pediatric and adolescent patients. They are rare in Western countries, but are more common in East Asia. We conducted this review and meta-analysis of existing evidence to evaluate the treatment condition and prognosis of IGCT in China and explore the associated problems and challenges.

Methods: The analysis was carried out with a search of the PubMed, Embase, Wanfang Data, and CNKI databases for literature published until October 2020. Only clinical studies and case reports in China with a pathological diagnosis containing a treatment protocol and long-term survival data of at least 18 months were included in the review. All patients were children or adolescents younger than 24 years old. This meta-analysis examined overall survival (OS) and progression free survival (PFS) at 3 years. The outcomes were pooled using a random effects model. We used the standardized critical appraisal instrument from the Joanna Briggs Institute (JBI) to assess the risk of bias.

Results: The final search included 9 studies with 218 patients. The pooled 3-year PFS of patients with germinomas was 98% and of non-germinomatous germ cell tumors (NGGCTs) was 68% in the included studies. For germinomas, the pooled 3-year PFS and OS revealed that combined chemotherapy has a higher efficacy than therapy with radiation alone (100% *vs.* 90%, P=0.0415; 100% *vs.* 92%, P=0.0396).

Conclusions: Patients with germinomas can receive satisfying outcomes, and combined chemotherapy can provide better survival than radiation therapy alone. Further effort is needed in the future to improve survival in the children with IGCTs, with multidisciplinary input being the key to achieving satisfactory outcomes.

Keywords: Intracranial; germ cell tumor; China

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Introduction

Low- and middle-income countries bear 80% of the global cancer incidence and face unique challenges in coping with this disease. China has a pediatric population of 271 million, and approximately 45,000 new childhood cancers are diagnosed each year (1), thousands of which are central nervous system tumors. Despite great improvement achieved in acute lymphoblastic leukemia and some solid tumor in China, central nervous system tumors have long been ignored, with their unique challenges remaining unresolved.

Intracranial germ cell tumors (IGCT) are rare neoplasms occurring predominantly in pediatric and adolescent patients and which can be classified histologically into germinomas and non-germinomatous germ cell tumors (NGGCTs, including teratoma, choriocarcinoma, yolk sac tumor, and embryonal carcinoma). They are rare in

western countries, but more common in East Asia. Among brain tumor patients under the age of 20, international data shows an overall incidence of 3.9% in the USA and 16.9% (population-based) in Japan (2,3). Our data from several large centers suggest that, among brain tumor patients under the age of 18 in China, 7.27–21.1% (hospital-based) are diagnosed as IGCT (4-9).

Few articles have been published concerning the treatment of IGCT in China, especially for children. Therefore, we conducted this review and meta-analysis of existing evidence to evaluate the treatment condition and prognosis of IGCT in China and to explore the country's unique problems and challenges in this area.

Diagnostic methods of IGCT vary with countries and years. Some countries rely on surgical pathology for diagnosis, often with a gross total resection. In other countries, germ-cell tumors are not diagnosed with surgery but on the basis of select tumor markers. An increase in alpha-fetoprotein or human chorionic gonadotropin (HCG) to greater than a defined threshold in serum or cerebrospinal fluid can confirm the diagnosis of a secreting NGGCT. However, marker thresholds vary across countries. Before 2015, some hospitals in China preferred radiosensitivity testing (trial RT) or chemosensitivity testing without biopsy to make a germinoma diagnosis for marker-negative patients. In one study, patients were treated with 20 Gy of RT, and a presumed diagnosis of germinoma was made if a marked response (>80% shrink) was observed on follow-up (10). It was the same case in Korea (11), though according to the 4th International CNS germ cell tumor symposium, surgical biopsy is reserved for patients who are marker-negative (12). Because of the diversity of diagnostic methods in China and the fact that results are difficult to compare, in our study, we selected patients with confirmed pathology results. We present the following article in accordance with the PRISMA reporting checklist (available at https://pm.amegroups.com/article/view/10.21037/pm-21-32/rc).

Materials and methods

Search strategy

The analysis was carried with a search of the PubMed, Embase, Wanfang Data, and CNKI databases for literature published period until October 2020. The languages were limited to English and Chinese. The search strategy involved both Medical Subject Headings (MeSH) terms and keywords, including *germinoma*, *germ cell tumor*, *intracranial*, *central nervous system*, *brain*, and *China*. All References in articles were scanned to identify all relevant articles. The PubMed search history is available in Table S1.

Inclusion and exclusion criteria

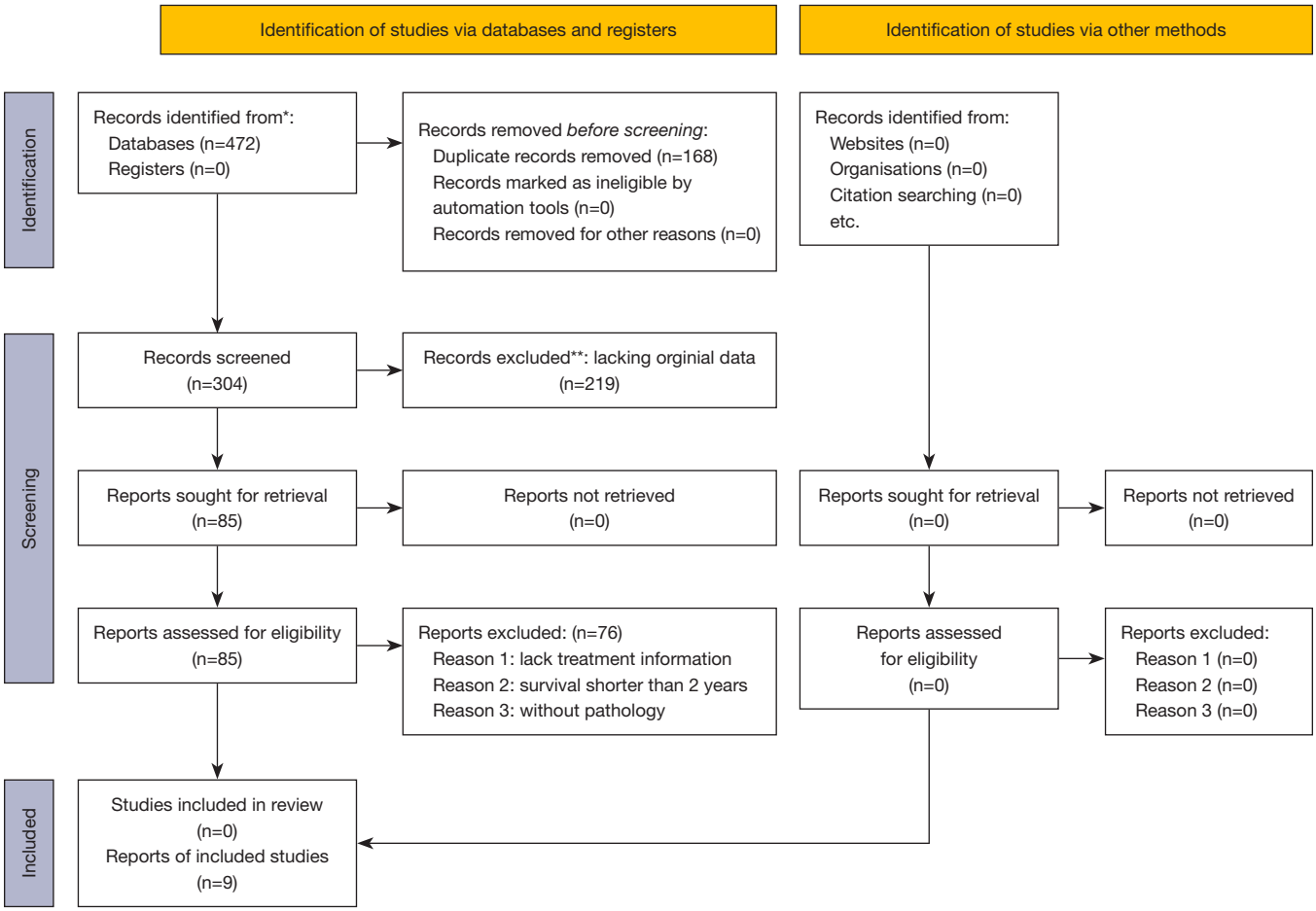
Only clinical studies and case reports in China containing treatment protocols focusing on patients with a pathological diagnosis and a median duration of follow-up of at least 18 months were included in the review. All patients were children or adolescents younger than 24 years. The selection process is illustrated in *Figure 1*. Data were reviewed by 2 reviewers independently. Disagreement between the reviewers was settled by a third reviewer. From the 472 articles found, 168 articles were removed as duplicates and 219 articles were excluded for lacking original data, being animal or adult studies, or otherwise being considered not relevant according to a reading of the titles and abstracts. Consequently, 85 articles were retrieved for further assessments according to the full text, 70 of which were excluded because they lacked treatment information and 6 of which were excluded for not having confirmation of the pathology. Finally, 9 studies (9,13-20) that met the inclusion criteria were included in the analysis.

Risk of bias assessment

Data related to the study and quality assessment were scrutinized by 2 reviewers independently. Disagreement between the reviewers was settled by a third reviewer. For case series, we used the standardized critical appraisal instrument from the Joanna Briggs Institute (JBI; Table S2).

Statistical analysis

Outcomes of interest were overall survival (OS) and progression-free survival (PFS). Data in the tables, texts, or figures of the original papers were extracted if the outcomes were not reported directly in the original paper. Continuous data are expressed as mean ± SD. The event rates were pooled using the random effects model. The inverse variance method was used to compare the outcomes. All P values were 2-sided, and a P value <0.05 was considered significant. Statistical calculations were performed using R software version 4.0 (The R Foundation for Statistical Computing).



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Figure 1 Flow diagram presenting study selection in the review.

Results

Characteristics of studies

The review is presented in the flow diagram (*Figure 1*). A total of 9 reports comprising 218 patients were included in the review (*Table 1*) (9,13-20). There were 75 female and 143 male patients analyzed. Mean age at diagnosis was 10.5±4.6 years (range, 3–24 years). There were 118 germinomas and 100 NGGCTs. The most common tumor site was the suprasellar region (35.3%), followed by the pineal area (26.1%), and other locations (25.0%), including the basal ganglia, thalamus, third ventricle, and cerebellum. In addition, 29 cases were multifocal tumors including 13 cases (6%) that were bifocal tumors (suprasellar and pineal area).

For the survival analysis, 6 reports including 97 germinomas were analyzed (9,13-16,18) and 6 reports including 78 NGGCTs were analyzed (13,16-20). For germinoma, the total number of the patients in the radiotherapy (RT)-alone group and the radiotherapy combined with chemotherapy (CMT) group were 38 and 59, respectively. In the CMT group, whole brain (WB), whole ventricle (WV), or craniospinal irradiation (CSI) was applied, with 20–36 Gy was given in WB/WV/CSI and 10–49 Gy was given in tumor-bed boost. The chemotherapy protocol included 2–6 cycles of carboplatin, etoposide, cisplatin and ifosfamide; or vinblastine, bleomycin, cisplatin and etoposide. In the RT-only group, focal irradiation and/

Table 1 Characteristics of the study

Author, year	Patients (n)	Age [years]	Male (%)	Diagnosis	Study design	Location	Follow-up [median/months]
Zhang 2018	52	10.8 [1–18]	0.5	Pathology	Case series	Beijing, multicenter	30 [8–53]
Dong 2019	43	6.0 [3.6–15.5]	0.7	Pathology	Case series	Shanghai, single center	31.8 [1–144]
Zhao 2017	16	11.1 [3–24]	0.6	Pathology	Case series	Beijing (Tsinghua University), single center	17.5 [4–45]
Wanggou 2012	29	13.0 [6–24]	0.7	Pathology	Case series	Changsha, single center	54 [5–60]
Wong 2008	6	10.9 [9.3–13.6]	1.0	Pathology	Case series	Taipei, single center	143 [73–190]
Wang 2018	11	11.9 [7–16]	0.8	Pathology	Case series	Chengdu, single center	36 [9–72]
Tang 2007	14	12.4 [8–18]	0.9	Pathology	Case series	Beijing (Tiantan Hospital), single center	56 [6–87]
Xiao 2011	15	16.3 [8–24]	1.0	Pathology	Case series	Guangzhou, single center	24 [4–120]
Lian 2014	32	9.5 [6–14]	0.5	Pathology	Case series	Beijing (Peking Union Medical College), single center	60 [4–216]

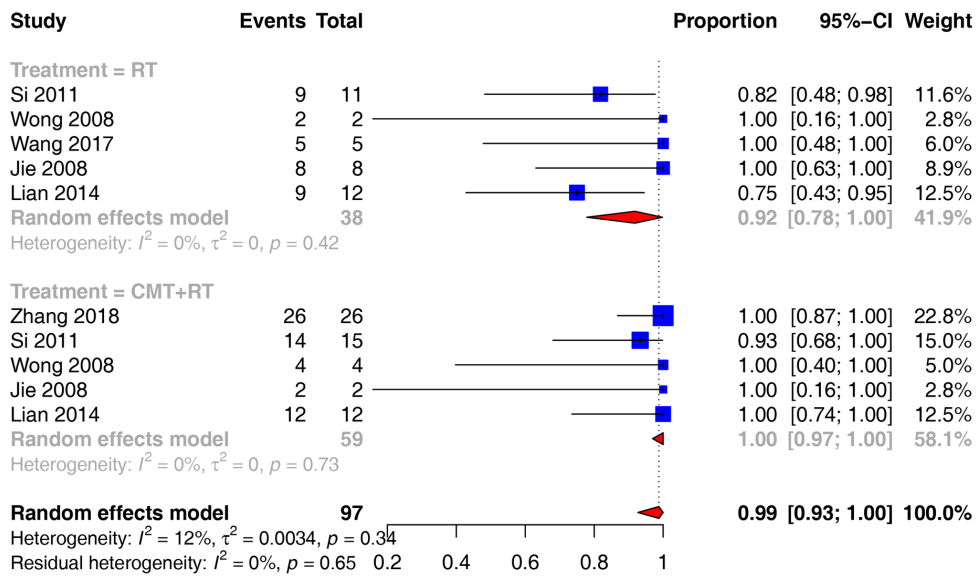


Figure 2 The 3-year overall survival rates comparing the RT only and RT combined with chemotherapy treatment of the included studies on germinomas. RT, radiotherapy.

or CSI/WB/WV was applied with the radiation dose ranging from 40 to 50 Gy in focal irradiation and 20 to 38 Gy in WB/CSI/WV.

For NGGCTs, 78 patients were included. Some patients received chemotherapy combined with surgery and others received chemotherapy, radiation, and surgery. The chemotherapy protocol included 2–6 cycles of etoposide, cisplatin and ifosfamide. The radiation strategy included local irradiation, WB radiotherapy, WV radiotherapy, CSI, and local radiation plus WV/WB/CSI. The radiation dose ranged from 29 to 55 Gy in focal irradiation and from 17.8 to 39.6 Gy in WB/CSI/WV. Some studies (13,17,18,20) did not describe the radiation doses.

Meta-analysis

The main results of this meta-analysis are shown in *Figures 2-4* and summarized in *Table 2*. According to

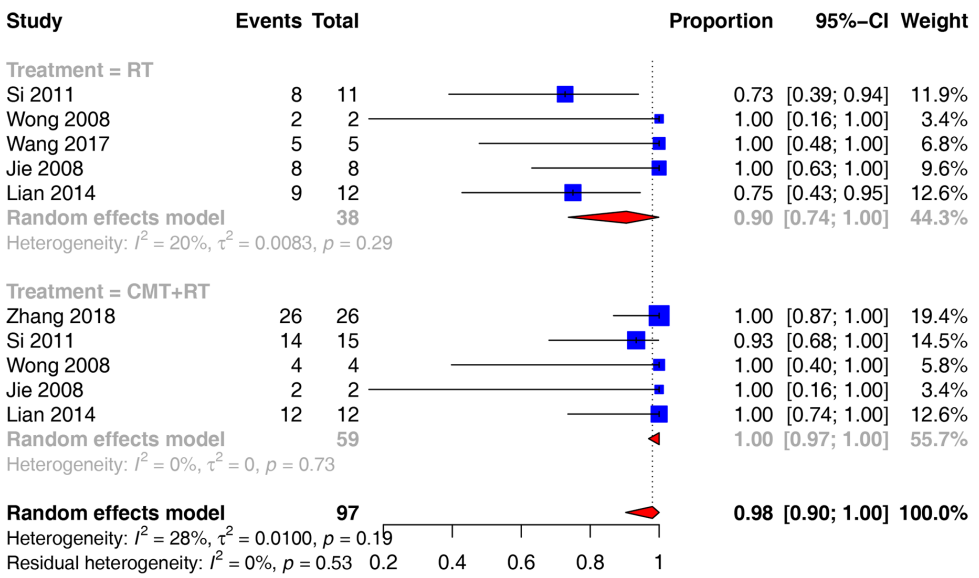


Figure 3 The 3-year progression-free survival rates comparing the RT only and RT combined with chemotherapy treatment of the included studies in germinomas. RT, radiotherapy.

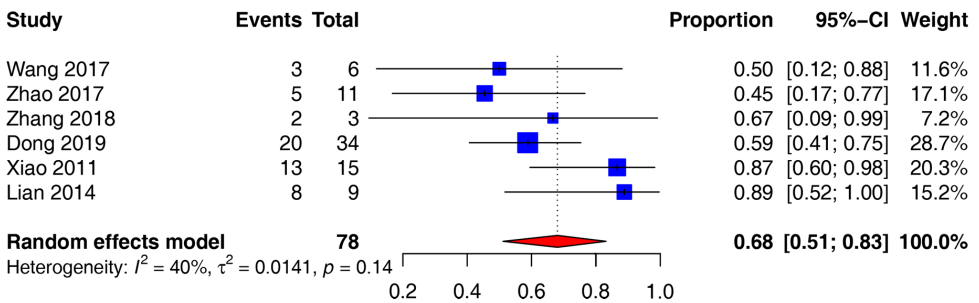


Figure 4 The 3-year progression-free survival rates of the included studies for non-germinomatous germ cell tumors.

the data available, we collected the 3-year PFS rate and OS rate.

The pooled 3-year PFS and OS for germinoma revealed by a random effects model of the CMT + RT group was higher than that of the RT-only group (100% *vs.* 90%, P=0.0415; 100% *vs.* 92%, P=0.0396). In the included studies, the pooled 3-year PFS of germinoma was 98% while that of NGGCT was 68%.

Discussion

IGCTs include germinomas and NGGCTs. Intracranial germinomas account for two-thirds of IGCTs. Radiotherapy including craniospinal RT was once the standard treatment for intracranial germinoma, and the cure rate for RT monotherapy exceeds 90%. Because of the severe side effects, such as neurocognitive impairment and endocrinopathies, in some centers chemotherapy combined with radiotherapy has been attempted to enable reduction in both RT dose and volume. The consensus on IGCTs in 2015 pointed that aim in germinoma treatment is to maintain an excellent OS rate while attempting to minimize late effects. It was further suggested that radiotherapy include focal fields and at least the ventricles, and chemotherapy is an effective strategy to reduce the dose of radiotherapy for localized germinomas (12). In our meta-analysis, both the RT and chemotherapy combined groups gained satisfying outcomes, while the chemotherapy combined groups achieved better survival. The 3-year PFS and OS for germinoma were 99% and

Table 2 Summary of meta-analysis results

	Treatment	Outcome	95% CI	I^2	Heterogeneity P value	Difference between groups P value
Germinoma						
3-year PFS	ANY	0.98	(0.9, 1)	28%	0.19	
	RT	0.9	(0.74, 1)	20%	0.29	0.0415
	CMT + RT	1	(0.97, 1)	0%	0.73	
3-year OS	ANY	0.99	(0.93, 1)	12%	0.34	
	RT	0.92	(0.78, 1)	0%	0.42	0.0396
	CMT + RT	1	(0.97, 1)	0%	0.73	
NGGCT						
3-year PFS	ANY	0.68	(0.51–0.83)	40%	0.14	

PFS, progression free survival; ANY, any treatment including radiotherapy and chemotherapy, including all the patients; RT, radiotherapy; CMT, radiotherapy combined with chemotherapy; OS, overall survival; NGGCT, non-germinomatous germ cell tumor.

98%, respectively. The SMC-G13 trial demonstrated that induction chemotherapy reduces radiation therapy dose and volume in intracranial germinomas (21). Patients received 4 cycles of chemotherapy with carboplatin/etoposide alternating with cyclophosphamide/etoposide. A dose of 18 Gy of craniospinal RT for metastatic tumors, whole ventricle RT for localized tumors followed by 12.6 Gy boost RT to the primary tumor bed was administered after chemotherapy. The 5-year PFS and OS was 96.7% and 96.2%, respectively. Therefore, we suggest that for patients with pure germinomas, chemotherapy combined therapy would be a better choice to enable reduction in both RT dose and volume.

Patients with NGGCT had worse outcomes compared with those with germinoma. The 5-year OS in patients with NGGCT treated with radiation alone or chemotherapy alone ranged from 20% to 40% (22). For patients with IGCT containing malignant non-germinomatous components, the consensus points out that a combination of chemotherapy and RT be applied to maximize the chance of cure (12). In our study, the 3-year PFS for NGGCT was 68%, but the data were not convincing due to the considerable heterogeneity in chemotherapy doses and volumes. The recent international COG ACNS0122 trial and SIOP CNS GCT 96 trial have reported encouraging results. The COG ACNS0122 trial used 6 cycles of chemotherapy of 36 Gy CSI and 54 Gy to the primary tumor bed (23). The 5-year PFS and OS were 84% and 93%, respectively. The SIOP trial 96 used 4 cycles of chemotherapy for those with localized disease, with a 54 Gy dose being administered to the involved field (24). The 5-year PFS and OS were 72% and 82%, respectively.

Although there are many patients (at least 531 according to the populations reported) diagnosed with IGCT every year, (218/20 years) few patients receive proper treatment in China. Many unique challenges exist in the pediatric neuro-oncology service in China. Lack of well-trained pediatric neuro-oncologists, lack of multidisciplinary care teams, high rates of midtreatment abandonment, lack of adequate knowledge of IGCTs, and lack of children's hospitals for pediatric patients with central nervous system tumors (without basic RT facilities in any children's hospital in China) remain the key challenges in China (1). This is frustrating for patients and their families who may receive a confusing array of opinions, leading to delays for adjuvant chemotherapy or radiation after surgery, or even abandonment. Even in Shanghai, before 2017, due to a lack of well-trained pediatric neuro-oncologists, most pediatric central nervous system tumor patients were admitted to adult hospitals. Since October 2017, after cooperation began with St. Jude Children's Research Hospital, Shanghai Children's Medical Center began receiving children with central nervous system tumors. We began receiving IGCT patients in October 2018. The COG's ACNS1123 protocol was adopted in our center. Thus far, we have received 105 children with brain tumors, with 40 of these cases being IGCTs: 7 were germinomas, and the other 33 were NGGCTs. Of these 40 patients, 10 were girls and 30 were boys, with the endian age at diagnosis being 10 years (range, 2 months to 16 years). For

germinoma, 4 patients received RT alone after surgery, and another 3 patients received 4 cycles of chemotherapy with carboplatin and etoposide before radiation (24 Gy WV and 16 Gy local tumor boost). All 7 patients remained in complete remission after a median follow-up of 12 months (range, 2–25 months). For NGGCTs, 33 patients received 6 cycles of chemotherapy with carboplatin and etoposide being alternated with ifosfamide and etoposide. After chemotherapy, the patient was evaluated to determine whether they receive radiation (36 Gy CSI and 54 Gy local tumor boost), second surgery, or autologous stem cell transplantation. One patient abandoned treatment halfway, 2 patients relapsed after half a year and 1 year respectively, 14 patients are still receiving treatment, and the remaining 16 patients were surviving after a median follow-up of 15 months (range, 11–24 months).

The deficiencies in treatment in China emphasized the necessity in establishing multidisciplinary care teams in pediatric hospitals receiving children with central nervous system tumors. The treatment of pediatric and adolescent IGCTs requires close collaboration with interdisciplinary teams consisting of neurosurgeons, radiologists, pathologists, radiation oncologists, and pediatric neuro-oncologists. And a national treatment protocol/study would also be useful to standardize treatment within China. Great effort needs to be made in the future to improve IGCT outcomes.

Some limitations to our analysis should be mentioned. First, studies included were few in number and noncomparable, and the I^2 statistics indicated a high publication bias, which weakens the evidence based on the results drawn. Second, across the different groups, the choice of treatment strategy varied, including the radiation dose and fields, as well as the chemotherapy drugs and doses, which increased the heterogeneity of the pooled outcomes and limited the validity of the conclusion. Third, other limitations include level of tumor markers, e.g., AFP <1,000 *vs.* >1,000 ng/mL; response to chemotherapy before radiotherapy; residual lesion with/without 2nd look surgery, which we did not mentioned in our context.

Overall, greater effort is needed in the future to improve survival in children with IGCTs, and multidisciplinary input is key to achieving satisfactory outcomes.

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Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Ibrahim Qaddoumi, Anthony Liu and Chenchen Sun) for the series "Pediatric CNS Tumors in China" published in *Pediatric Medicine*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://pm.amegroups.com/article/view/10.21037/pm-21-32/rc

Peer Review File: Available at https://pm.amegroups.com/article/view/10.21037/pm-21-32/prf

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at https://pm.amegroups.com/article/view/10.21037/pm-21-32/coif). The series "Pediatric CNS Tumors in China" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Pak-Yin Liu A, Moreira DC, Sun C, et al. Challenges and opportunities for managing pediatric central nervous system tumors in China. Pediatr Investig 2020;4:211-7.
2. Ostrom QT, Gittleman H, Fulop J, et al. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008-2012. Neuro Oncol 2015;17 Suppl 4:iv1-62.

3. Takami H, Fukuoka K, Fukushima S, et al. Integrated clinical, histopathological, and molecular data analysis of 190 central nervous system germ cell tumors from the iGCT Consortium. Neuro Oncol 2019;21:1565-77.
4. Gui T, Zhang QH, Zhang TG, et al. Central nervous system tumors in childhood: analyses of 330 cases. Chinese Journal of Clinical and Experimental Pathology. 2008;24:403-6.
5. Zhang R, Shen WQ, Zhou LF. Primary pediatric central nervous system tumors statistic: study of 763 cases in a single institution. Zhonghua Yi Xue Za Zhi 2007;87:442-7.
6. Zhu T, Yu YH, Zhang DJ, et al. Clinical analysis of central nervous system tumors in children: a report of 468 cases. Chinese Journal of neurosurgery 2012;28:8-12.
7. Wang J, Zhao YY, Yang JY, et al. Clinal analysis of pediatric central neuvous system tumors: a retrospctive study of 219 cases. Guangdong Medical Journal. 2015;36:2621-4.
8. Li JZ, Chu H, Miao N, et al. Pediatric tumors of nervous system tumors: a clinicopathologic study of 398 cases. Chinese Journal of diagnostic Pathology. 2019;26:333-7.
9. Wong TT, Chen YW, Guo WY, et al. Germinoma involving the basal ganglia in children. Childs Nerv Syst 2008;24:71-8.
10. Gao JM, Zhang Y, Zheng MM. Long-term results of radiotherapy for intracranial germinomas. Shanxi Medical Journal. 2006;35:546-8.
11. Byun HK, Yoon HI, Cho J, et al. Optimization of Intracranial Germinoma Treatment: Radiotherapy Alone with Reduced Volume and Dose. Int J Radiat Oncol Biol Phys 2020;108:657-66.
12. Murray MJ, Bartels U, Nishikawa R, et al. Consensus on the management of intracranial germ-cell tumours. Lancet Oncol 2015;16:e470-7.
13. Wang M, Zhou P, Zhang S, et al. Clinical features, radiologic findings, and treatment of pediatric germ cell tumors involving the basal ganglia and thalamus: a retrospective series of 15 cases at a single center. Childs Nerv Syst 2018;34:423-30.
14. Wanggou S, Jiang X, Yuan X, et al. Prognostic value of OCT4 in primary intracranial germinoma: a single institute analysis of 31 cases. Br J Neurosurg 2012;26:237-46.
15. Tang J, Ma Z, Luo S, et al. The germinomas arising from the basal ganglia and thalamus. Childs Nerv Syst 2008;24:303-6.
16. Lian X. A retrospective study of suprasellar tumor-like lesions and intracranial germinomas. [Master]: Peking Union Medical College; 2014.
17. Xiao G. Clinic and pathology characteristics research of pineal region mixed germ cell tumor. [Master]: Southern Medical University; 2011.
18. Zhang LJ, Zhao XJ, Xiao J, et al. Diagnosis, treatment and follow-up of 52 cases of primary intracranial germ cell tumors diagnosed by pathology under the multidisciplinary collaboration. Journal of China Pediatric Blood and Cancer 2018;23:178-83.
19. Dong XS, Yang J, Han YF, et al. The treatment and prognosis of primary pediatric intracranial nongerminomatous malignant germ cell tumors. Chinese Journal of Neurosurgery 2019;35:776-81.
20. Zhao YP, Zhang YQ, Duan HY, et al. Intracranial mixed germ cell tumor. Zhonghua Yi Xue Za Zhi 2017;97:661-5.
21. Lee JW, Lim DH, Sung KW, et al. Induction Chemotherapy Reduces Radiation Therapy Dose and Volume in the Treatment of Intracranial Germinoma: Results of the SMC-G13 Trial. Int J Radiat Oncol Biol Phys 2020;108:649-56.
22. Fangusaro J, Wu S, MacDonald S, et al. Phase II Trial of Response-Based Radiation Therapy for Patients With Localized CNS Nongerminomatous Germ Cell Tumors: A Children's Oncology Group Study. J Clin Oncol 2019;37:3283-90.
23. Goldman S, Bouffet E, Fisher PG, et al. Phase II Trial Assessing the Ability of Neoadjuvant Chemotherapy With or Without Second-Look Surgery to Eliminate Measurable Disease for Nongerminomatous Germ Cell Tumors: A Children's Oncology Group Study. J Clin Oncol 2015;33:2464-71.
24. Calaminus G, Frappaz D, Kortmann RD, et al. Outcome of patients with intracranial non-germinomatous germ cell tumors-lessons from the SIOP-CNS-GCT-96 trial. Neuro Oncol 2017;19:1661-72.

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Supplementary

Table S1 The PubMed search history

Search number	Query	Sort By	Filters	Search details	Results	Time
11	((((Germinomas[Title/Abstract]) OR (germ cell tumor[Title/Abstract])) OR ("Germinoma"[Mesh])) AND ((((intracranial[Title/Abstract]) OR (central nervous system[Title/Abstract])) OR (brain[Title/Abstract])) OR ("Brain"[Mesh]))) AND (China)			("Germinomas"[Title/Abstract] OR "germ cell tumor"[Title/Abstract] OR "Germinoma"[MeSH Terms]) AND ("intracranial"[Title/Abstract] OR "central nervous system"[Title/Abstract] OR "Brain"[Title/Abstract] OR "Brain"[MeSH Terms]) AND ("China"[MeSH Terms] OR "China"[All Fields] OR "China s"[All Fields] OR "Chinas"[All Fields])	103	0:49:33
10	China			"China"[MeSH Terms] OR "China"[All Fields] OR "China s"[All Fields] OR "Chinas"[All Fields]	1,826,300	0:47:12
9	(((intracranial[Title/Abstract]) OR (central nervous system[Title/Abstract])) OR (brain[Title/Abstract])) OR ("Brain"[Mesh])			"intracranial"[Title/Abstract] OR "central nervous system"[Title/Abstract] OR "Brain"[Title/Abstract] OR "Brain"[MeSH Terms]	1,883,459	0:46:13
8	"Brain"[Mesh]	Most recent		"Brain"[MeSH Terms]	1,213,696	0:43:09
7	((Germinomas[Title/Abstract]) OR (germ cell tumor[Title/Abstract])) OR ("Germinoma"[Mesh])			"Germinomas"[Title/Abstract] OR "germ cell tumor"[Title/Abstract] OR "Germinoma"[MeSH Terms]	14,439	0:39:36
5	"Germinoma"[Mesh]	Most recent		"Germinoma"[MeSH Terms]	11,131	0:38:21
6	(("Germinoma"[Mesh]) OR (germ cell tumor*[Title/Abstract])) OR (germinoma[Title/Abstract])			"Germinoma"[MeSH Terms] OR "germ cell tumor*"[Title/Abstract] OR "Germinoma"[Title/Abstract]	18,260	0:35:58
3	Germinoma			"germinoma"[MeSH Terms] OR "germinoma"[All Fields] OR "germinomas"[All Fields]	11,924	0:22:15
4	Germ cell tumor			"germ cell tumour"[All Fields] OR "neoplasms, germ cell and embryonal"[MeSH Terms] OR ("neoplasms"[All Fields] AND "germ"[All Fields] AND "cell"[All Fields] AND "embryonal"[All Fields]) OR "germ cell and embryonal neoplasms"[All Fields] OR ("germ"[All Fields] AND "cell"[All Fields] AND "tumor"[All Fields]) OR "germ cell tumor"[All Fields] OR "germinoma"[MeSH Terms] OR "germinoma"[All Fields] OR ("germ"[All Fields] AND "cell"[All Fields] AND "tumor"[All Fields])	354,400	0:17:29
2	Incracranial germonima China			"incracranial"[All Fields] AND ("China"[MeSH Terms] OR "China"[All Fields] OR "China s"[All Fields] OR "Chinas"[All Fields])	0	22:16:50
1	Intracranial germinoma China			("intracranial"[All Fields] OR "intracranially"[All Fields]) AND ("germinoma"[MeSH Terms] OR "germinoma"[All Fields] OR "germinomas"[All Fields]) AND ("China"[MeSH Terms] OR "China"[All Fields] OR "China s"[All Fields] OR "Chinas"[All Fields])	59	22:16:50

Table S2 Critical appraisal results using JBIst

Study	Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Outcome
Zhang	2018	Y	Y	U	Y	Y	Y	Y	Y	Y	Include
Dong	2019	Y	Y	Y	Y	U	Y	N	Y	Y	Include
Zhao	2017	Y	Y	Y	Y	U	Y	Y	Y	Y	Include
Wang	2017	Y	Y	U	Y	Y	Y	Y	Y	Y	Include
Xiao	2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	Include
Lian	2014	Y	Y	Y	Y	Y	Y	Y	Y	Y	Include
Tang	2007	Y	Y	U	Y	Y	Y	Y	Y	Y	Include
Wong	2008	Y	Y	Y	Y	U	Y	Y	Y	Y	Include
Wanggou	2012	Y	Y	U	Y	U	Y	Y	Y	Y	Include

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