


Epidemiology, Management, and Long-Term Survival Outcomes of Intracranial Typical Site Germinomas: An Analysis of the Surveillance, Epidemiology, and End-Results (SEER) Database

Cancer Control
Volume 29: 1–9
© The Author(s) 2022
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/10732748221095944
journals.sagepub.com/home/ccx


Wenqiang Che, MD, PhD^{1,2,*}, Yujiao Wang, MD, PhD^{3,*}, Yanmin Zhou, MD^{1,*},
Xiangyu Wang, MD, PhD¹ , and Jun Lyu, MD, PhD² 

Abstract

Background: The correlations of epidemiological characteristics and clinical outcomes with different tumor sites in patients with intracranial typical site germinomas (ICTSGs) have not yet been well established. We analyzed ICTSGs using a multicenter database, focusing on its demographic, management patterns, and long-term survival outcomes.

Methods: Patients diagnosed with ICTSGs were selected from the Surveillance, Epidemiology, and End-Results (SEER) database. Demographic information and management patterns of ICTSGs were extracted for data analysis stratified by different tumor sites. Kaplan–Meier curves were used to evaluate the survival outcome stratified by treatment, tumor site and tumor size.

Results: Among the 327 patients enrolled in the study, 16.21% had tumors located in the suprasellar region and 83.79% in the pineal region. The proportion of males was significantly higher among pineal germinomas (94.16 vs 66.04%; $P < .001$). Smaller tumors (<24 mm) were more common in the suprasellar region (37.74 vs 18.87%; $P < .001$). A higher percentage of patients with suprasellar germinomas underwent surgery. Radiotherapy (RT) and chemotherapy (CT) was, respectively, administered to 82.97 and 60.61% of patients during the treatment period, with no significant difference between suprasellar and pineal germinomas. CT plus RT was the most common treatment modality for both pituitary (30.19%) and pineal (33.94%) germinomas. Both RT and CT were associated with improved long-term survival. No survival difference was observed between suprasellar and pineal germinomas.

Conclusions: Despite significant differences in epidemiology and management, pineal and suprasellar germinomas had a similar long-term clinical outcome.

Keywords

germinomas, pineal gland, suprasellar, prognosis, SEER

¹Department of Neurosurgery, The First Affiliated Hospital of Jinan University, Guangzhou, China

²Department of Clinical Research, The First Affiliated Hospital of Jinan University, Guangzhou, China

³Department of Pathology, Xuanwu Hospital, Capital Medical University, Beijing, China

*Che W, Wang Y, and Zhou Y contributed equally to this work.

Corresponding Authors:

Jun Lyu, Department of Clinical Research, The First Affiliated Hospital of Jinan University, No. 613, West Huangpu Avenue, Tianhe District, Guangzhou 510630, China.

Email: lyujun2020@jnu.edu.cn

Xiangyu Wang, Department of Neurosurgery, The First Affiliated Hospital of Jinan University, 613 W.Huangpu Avenue, Guangzhou 510630, China.

Email: wang_xy123@126.com



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and

Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

Introduction

Intracranial germinomas are rare primary central nervous system (CNS) tumors in western countries that account for 65–75% of all intracranial germ cell tumors (iGCTs).^{1,2} Germinomas predominantly occurs in male pediatric and young adult patients. The most common region affected by this neoplasm are the midline structures, such as the pineal gland and suprasellar region, which is why they are collectively referred to as intracranial typical site germinomas (ICTSGs).³ However, the correlations of epidemiological characteristics and clinical outcomes with different tumor locations have not yet been investigated in detail for ICTSGs.

Medical presentations and tumor markers are used to diagnose germ cell tumors in North America and Europe.³ However, since the majority of intracranial germinomas are non-secretory, the serum tumor marker levels (b-hCG and AFP) may be within the normal range in the early stage.⁴ Motor disorders (dyskinesia/ataxia and focal/general weakness), Parinaud syndrome (eye coordination disturbances and pupil dysfunction), neurological manifestations (headache, nausea/vomiting, dizziness/vertigo, and drowsiness), polyuria/polydipsia, and urine/stool incontinence have all been identified as possible symptoms in studies of ICTSGs.⁵ However, no characteristic clinical manifestations were observed, and early detection is difficult.

Germinomas are highly sensitive to radiotherapy (RT) and chemotherapy (CT).^{6,7} However, it is worth noting that all confirmed cases of recurrence were located outside of the irradiated field in patients who received local radiation therapy, while there were no cases of observed recurrence following RT covering the ventricles.⁸ Both in terms of reducing the recurrence rate and prolonging survival, craniospinal radiation, whole-ventricle irradiation, or whole-brain RT gradually replaced local radiation therapy and have become the gold standard for treating germinomas.^{8–11} It became necessary to decrease the radiation dose due to the sequelae of CNS irradiation, such as cognitive impairment and hormonal dysfunction.¹² As a result, platinum-based CT has been adopted by an increasing number of medical centers. Compared to radiation alone, a combination regimen of RT and CT has also been found to provide better clinical outcomes.¹³ Nevertheless, there are a variety of treatment methods for integrating RT and CT, and the optimal regimen is still being researched.

ICTSGs outlive germinomas in atypical locales in terms of progression-free survival.³ However, the differences in epidemiological data and clinical outcomes between ICTSGs affecting different sites are mostly unknown and have previously only been described in a few studies of limited patient populations. Furthermore, previous research has not been able to properly clarify whether there are gaps in the WHO definition of ICTSGs or heterogeneity in outcomes across various treatment centers. In order to improve the clinical management of ICTSGs, we analyzed 327 cases selected from the Surveillance Epidemiology and End-Results (SEER) database, to

be further integrated with the epidemiological characteristics and long-term clinical outcomes.

Materials and Methods

Ethics Approval Statement

All patient data in the NCI SEER is anonymized, and the study received a waiver for consent from the ethics committee due to its retrospective nature and guaranteed patient privacy.

A Study Designed to Select Patients

We performed a retrospective analysis of the SEER program governed by the USA National Cancer Institute (NCI, USA). The SEER database collects and publishes data on cancer incidence, treatment, and survival from 18 cancer registries in 13 states (Alaska, California, Connecticut, Georgia, Hawaii, Iowa, Kentucky, Louisiana, Michigan, New Jersey, New Mexico, Vermont, and Washington) that covers around 30% of the US population and could readily represent the population diversity.¹⁴ A SEER Research Data Agreement was essential to obtain the user account, enabling free access to the SEER data. Individual-level data were extracted from the SEER database using NCI SEER*Stat 8.3.9 software published on March 15, 2021. Patients diagnosed after December 31, 2010, were eliminated in order to guarantee sufficient follow-up time. In 1998, the SEER database was updated to include detailed information on surgery for individuals diagnosed with systemic malignancies and patients diagnosed before 1/1/1998 were not included in the study. Thus, the cohort in the current study consisted of patients diagnosed with a germinoma in the suprasellar region or the pineal gland from 1998 to 2010 using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3), histology codes 9064/3 (germinoma), and the ICD-O-3 site codes C75.1 (pituitary) and C75.3 (pineal). Patients had to be excluded due to incomplete dates for survival. Participant follow-up ended December 31, 2016.

Patient Demographics and Treatment History

Patients were further stratified according to the tumor site, yielding a suprasellar and a pineal region group. Demographic variables such as age, race/ethnicity, sex, region of diagnosis, tumor size, survival time (months), and vital status were collected. Age was used as a continuous variable and expressed as the mean \pm standard deviation (SD). Treatment information containing surgery, RT, and CT was accessible in the SEER database. The surgical strategies were described in detail and categorized into 5 classifications: gross total resection (GTR), subtotal resection (STR), biopsy, no surgery, and others. Treatment comparison categories included the abovementioned surgical approaches plus RT and CT or not. Descriptive analysis was performed to compare the demographic and treatment characteristics of the suprasellar and

Table 1. Demographics of patients with intracranial typical site germinomas.

Characteristics	Total (%)	Pituitary (%)	Pineal (%)	P Value
All	327 (100)	53 (100)	274 (100)	—
Mean age (S.D.)	18.32 (8.45)	17.98 (9.65)	18.39 (8.20)	.750
Age	—			
Pediatric	197 (60.24)	32 (60.38)	166 (60.58)	.978
Adult	130 (39.76)	21 (39.62)	108 (39.42)	—
Sex	—			
Male	293 (89.60)	35 (66.04)	258 (94.16)	<.001
Race	—			
N-H* White	175 (53.52)	27 (50.94)	148 (54.02)	.442
N-H* Black	20 (6.12)	2 (3.77)	18 (6.57)	—
Hispanic	70 (21.41)	10 (18.87)	60 (21.90)	
Others	62 (18.96)	14 (26.42)	48 (17.52)	
Tumor size	—			
≤24	98 (29.97)	20 (37.74)	78 (28.47)	<.001
>24	150 (45.87)	10 (18.87)	140 (51.10)	—
Unknown	79 (24.16)	23 (43.40)	56 (20.44)	
Region	—			
West	228 (69.73)	38 (71.70)	190 (69.34)	.988
South	45 (13.76)	7 (13.21)	38 (13.87)	—
Midwest	21 (6.42)	3 (5.66)	18 (6.57)	
Northeast	33 (10.09)	5 (9.43)	28 (10.22)	
Status	—			
Alive	286 (87.46)	47 (88.68)	239 (87.23)	.770
Follow-up time (Months)*	119 (165-83)	121 (164-83)	108 (165.75-80.25)	.964

Follow-up time (months)* expressed as median (interquartile range, IQR). N-H, non-Hispanic.

pineal groups. We excluded patients who had incomplete information on surgery from the analysis of management. Overall survival was used as the primary endpoint in survival analysis. We performed Kaplan–Meier (K-M) survival analysis (or Kaplan–Meier product-limit estimates) to plot the survival curves.

Statistical Analysis and Analytic Methods

Chi-squared and Fisher's exact test were used to estimate the differences in demographics and therapies between the suprasellar and pineal groups. We applied the Log-rank test to assess the statistical significance in the survival curves produced by the K-M methodology.¹⁵ Two-tailed P values of less than .05 were considered to indicate statistical significance for comparisons.

Results

Demographic Characteristics of the Enrolled Patients

The available cohort demographics and treatment characteristics for all patients are shown in Tables 1 and 2, respectively. The workflow we mentioned above was summarized in Figure 1. Overall, our population-based cohort consisted of 327 patients, with 53 (16.21%) tumors located in the suprasellar region and 274 (83.79%) in the pineal region. Figure 2 shows the number of

patients according to age, and the peak of onset was seen around the age of 14. The mean (\pm SD) age of patients was 17.98 \pm 9.65 years in the suprasellar group and 18.39 \pm 8.20 in the pineal group. Males greatly outnumbered females in the overall patient population (89.60%, 293/327), with a significantly higher male/female ratio in the pineal (94.16%, 258/274) than in the suprasellar (66.04%, 35/53) group ($P < .001$). In general, large tumors (>24 mm) were more common in the overall patient population (45.87%). However, small tumors (\leq 24 mm) were more common in the suprasellar region than in the pineal region (37.74 vs 28.34%, $P < .001$). The median follow-up time for the entire cohort was 119 months (interquartile range (IQR) 169-83).

In terms of race/ethnicity, most patients were non-Hispanic White (53.52%) followed by Hispanic (21.41%), others (containing non-Hispanic Asian or Pacific Islander and non-Hispanic American Indian/Alaska Native, 18.96%), and non-Hispanic Black (6.12%). The United States (US) is divided into 4 geographical census regions in the database, and the Western part accounted for the majority of the patients (69.73%), followed by the Southern region (13.76%), Northeast region (10.09%), and Midwest region (6.42%).

Overall, there were no statistically significant differences between the suprasellar and pineal groups in age, race, geographic location and follow-up time. However, significant differences were found in the gender distribution ($P < .001$)

Table 2. Management patterns* of patients with intracranial typical site germinomas.

Characteristics	Total (%)	Pituitary (%)	Pineal (%)	P Value
Radiotherapy (RT)	—			
Yes	268 (82.97)	42 (82.35)	226 (83.10)	.898
Chemotherapy (CT)	—			
Yes	199 (60.61)	36 (70.59)	163 (59.92)	.151
Surgery	—			
GTR	26 (7.95)	8 (15.09)	18 (6.57)	.001
STR	34 (10.40)	11 (20.76)	23 (8.40)	—
Biopsy	57 (17.43)	10 (18.87)	47 (17.15)	
No	206 (63.78)	22 (41.51)	184 (67.15)	
Surgery	—			
Yes	117 (36.22)	29 (56.86)	88 (32.35)	<.001
Treatment comparison	—			
RT+CT	109 (33.33)	16 (30.19)	93 (33.94)	—
RT only	57 (17.43)	3 (5.66)	54 (19.71)	
Biopsy +RT+CT	28 (8.56)	4 (7.55)	24 (8.76)	
CT only	24 (7.34)	2 (3.77)	22 (8.03)	
STR+RT+CT	22 (6.73)	8 (15.09)	14 (5.11)	
Biopsy +RT	20 (6.12)	1 (1.89)	19 (6.94)	
No treatment	16 (4.89)	1 (1.89)	15 (5.47)	
GTR+RT	13 (3.98)	2 (3.77)	11 (4.02)	
GTR+RT+ CT	10 (3.06)	5 (9.43)	5 (1.83)	
STR+RT	9 (2.75)	3 (5.66)	6 (2.19)	
Biopsy only	6 (1.84)	4 (7.55)	2 (.73)	
Biopsy +CT	3 (.92)	1 (1.89)	2 (.73)	
GTR only	2 (.61)	1 (1.89)	1 (.37)	
STR+CT	2 (.61)	0 (.00)	2 (.73)	
GTR+CT	1 (.31)	0 (.00)	1 (.37)	
STR only	1 (.31)	0 (.00)	1 (.37)	

Available data for management patterns* n =323; RT, Radiotherapy; CT, Chemotherapy; GTR, gross total resection; STR, subtotal resection.

and tumor size ($P < .001$) between the suprasellar and the pineal germinomas.

Patient Treatment Characteristics

The treatment data were available for 323 patients. A total of 268 (82.97%) patients received RT as part of therapy, with no statistically significant difference ($P = .898$) between the suprasellar and pineal groups (82.35 vs 83.10%). CT was performed for 60.61% of all patients as part of therapeutic modality with not statistically significant ($P = .151$) usage difference in the suprasellar region (70.59%) when compared to the pineal region germinomas (59.92%). 117 (36.22%) patients underwent surgery as part of the treatment. There was a significantly higher rate of surgical treatment (including GTR, STR, and biopsy) in the suprasellar region than in the pineal region ($P = .001$). Treatment regimens for suprasellar germinomas most commonly included RT + CT (30.19%), RT + STR + CT (15.09%), and RT+GTR+CT (9.43%). For pineal germinomas, most patients underwent RT + CT (33.94%), followed by RT (19.71%) and RT + biopsy + CT (8.76%). We observed 54 (19.71%) and 22 (8.03%) pineal ICTCGs who

received RT only and CT only, respectively. This was accompanied by 3 (5.66%) and 2 (3.77%) suprasellar ICTCGs treated with RT only and CT only, respectively.

Overall Survival

Kaplan–Meier curves were plotted to compare the long-term survival among groups stratified by primary tumor site, tumor size, and treatments (Figure 3). There was no difference in survival between suprasellar and pineal germinomas ($P = .760$). The association of tumor size and overall survival in our cohort did not reach statistical significance. Furthermore, we found that RT ($P = .0048$) and CT ($P = .0053$) were significantly associated with increased overall survival. And the effect of radiation treatment, chemotherapy, and tumor location on the outcomes of patients who had surgery with verified tumor pathology was similar to the whole cohort (Supplemental Figure S1).

Discussion

The current study aimed to address the scarcity of data on the demographics and management of ICTSGs. At present, there

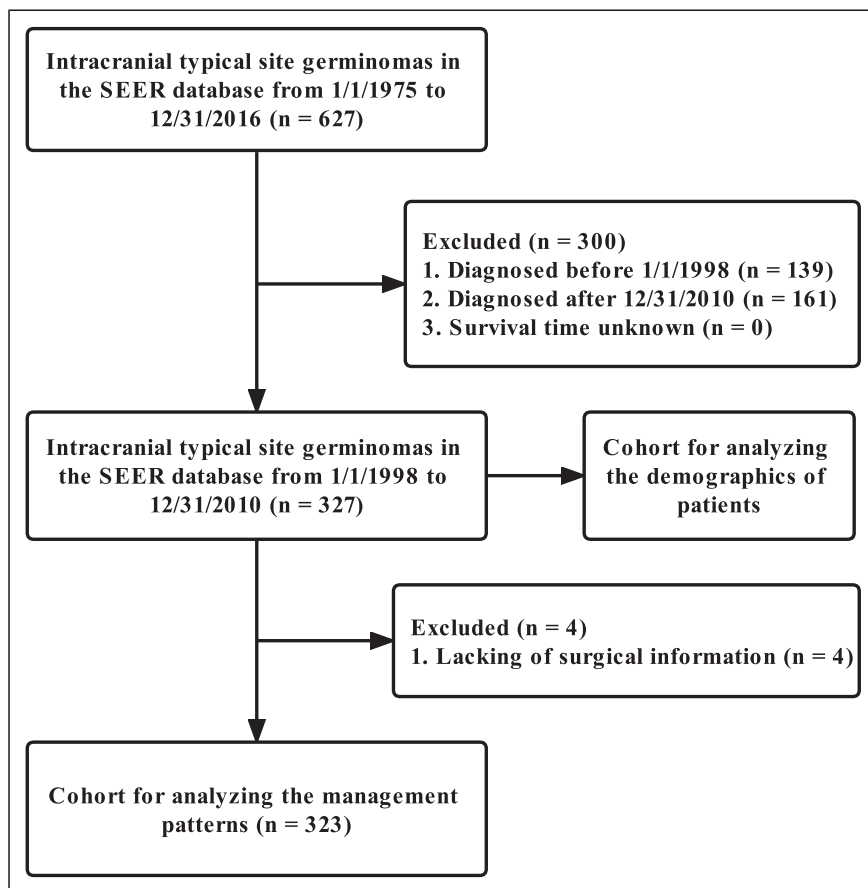


Figure 1. Workflow for the analysis of demographics and management patterns of patients with intracranial typical site germinomas.

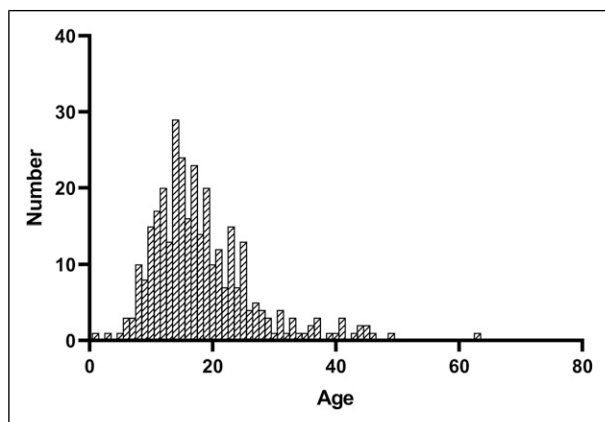


Figure 2. The number of patients with intracranial typical site germinomas.

are few extensive cohort studies that offer reliable insights for diagnosing and treating ICTSGs due to the low incidence of the disease. Midline tumors, also known as germinomas, a primary histological subtype of iGCTs, most frequently arise in the pineal and suprasellar regions, but the differences in their respective epidemiologically are not well described.

Our analysis demonstrates that the average onset age of suprasellar germinomas was similar to that of pineal germinomas (17.98 vs 18.39; $P = .750$). This suggests that the tumor location does not influence the age of onset. However, it is well known that the pathogenesis of germinomas depends on a patient's age.^{3,16,17} We observed 1 peak of occurrence of onset at the age of 14–15, and a similar trend was reported by Takami,¹⁸ who compared the difference of epidemiology, tumor location, histology, and prognosis of iGCTs between Mayo Clinic ($n = 98$) and Japanese consortium cohorts ($n = 154$) and observed a single peak during adolescence in both places. The “germ cell theory” which states that the faulty location of primordial germ cells occurs with a similar pattern intracranially and extracranially.¹⁹ On the way to the normal destination, primordial germ cells may abnormally migrate during the 3rd–4th week of gestation and inappropriately stay in midline structures, such as the mediastinum sacrococcygeal region and the third ventricle.^{20,21} The high incidence of adolescent cases of germinomas in this study needs more in-depth research in the future.

Suprasellar germinomas have a male predominance, with no apparent differences in pediatric and adult groups.²² Similarly, a male predominance was noted in neurohypophyseal and pineal germ cell tumors. The sex distribution was

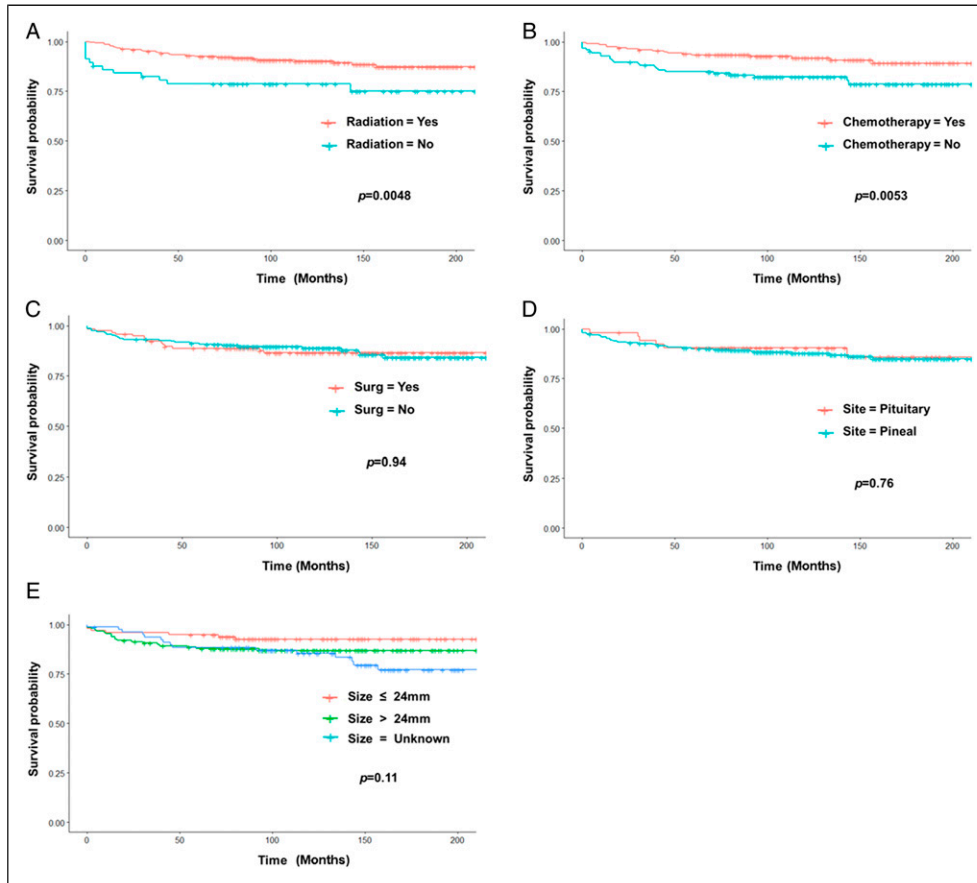


Figure 3. Kaplan–Meier curves showing a significantly improved long-term survival in patients receiving radiotherapy (A) or chemotherapy (B); surgical treatment (C) and tumor site (D) were not associated with patient survival; smaller tumor size (<24 mm) was related to better long-term survival, but the difference did not reach statistical significance (E).

more markedly skewed among patients with tumors in the pineal region, greater than 90% of which were male, compared with approximately 75% of patients in the neurohypophyseal region.⁸ However, the sample size ($n = 60$) of the study was small, which might influence the reliability of the results. Fortunately, the data of our study, which is based on NCI SEER with a larger sample size, consolidate these findings. Based on the “germ cell theory,” we hypothesized that progenitor germ cells appeared with equal frequency at pineal and suprasellar region in both sexes, and affected by physiological/hormonal changes in adolescence, tumorigenesis preferentially occurs in males in the pineal region. Alternatively, the pineal gland may have a unique developmental attraction for the abnormal aggregation of progenitor germ cells in males. Both these scenarios provide plausible explanations for our other finding that a higher proportion of large-sized tumors (>24 mm) occurred in the pineal region while smaller ones were mostly found in the suprasellar region. Although the high ratio of missing values of tumor size in the suprasellar region may affect the reliability of the results, the overall proportion of missing values was acceptable for complete case analysis.

Our findings indicated that the vast majority of the study cohort (82.57%) underwent RT not only in suprasellar germinomas but also in pineal germinomas, and more than half of the patients (60.86%) received CT in both suprasellar and pineal germinomas (67.93 and 59.50%, respectively). Similar RT administration ratios were observed in recent studies on iGCTs (germinomas and non-germinomatous tumors) as a whole²³ or germinomas only in the suprasellar region.²² Interestingly, Bhimani et al found that pediatric patients were significantly more prone to receive radiation therapy during treatment than adult patients (79.2 vs 41.0%). Therapies like these could be tailored to pediatric patients to minimize the long-term adverse effects of radiation on cognitive and endocrine dysfunction.^{12,24} However, we found that the overall administration ratio of CT (63%) reported by Bhimani et al was similar to the 1 found in our study (60.86%). These differences in treatment patterns might be related to patient age rather than primary tumor location. Local radiation therapy is a poor treatment for localized germinoma, and the Pediatric and Children’s Oncology Group of the European Society recommends whole-ventricle irradiation in combination with platinum-based CT.^{11,25} This explains our finding that RT plus

CT was the most commonly performed therapeutic methods in the entire cohort (33.33%), suprasellar cohort (30.19%), and pineal cohort (33.94%).

Moreover, patients with suprasellar germinomas were significantly more likely to receive surgery (including GTR, STR, and biopsy) than those with pineal germinomas (56.86 vs 32.35%). In fact, suprasellar germinomas can be challenging to diagnose, which is most likely to result in delayed diagnosis or misdiagnosis. It was reported that 82% of patients with suprasellar iGCTs experienced a delay in diagnosis ≥ 6 months.²⁶ A median time of about 16.8 months was needed to confirm the diagnosis of a pituitary tumor.²⁷ As a result, a histopathological diagnosis based on a surgical specimen is required. Therapies for iGCTs in Japan are usually based on postoperative histopathology diagnosis that divides patients into 3 risk groups.^{28,29} In the United States, on the other hand, it is more customary to establish a diagnosis based on clinical symptoms and tumor markers rather than a histology finding.³⁰ This means that if a germinoma is verified by initial laboratory findings, clinical manifestations, and MR imaging, the patients will receive the standard treatment (RT with or without CT). In present research, 1 unanticipated finding was that surgery was not associated with improved long-term survival results ($P = .94$). If a preoperative diagnosis for pituitary and pineal tumors is problematic, surgery is essential for a clear diagnosis, and the degree of surgery should also be addressed.³¹

The survival analysis suggested that both RT and CT improved the prognosis in the whole study cohort. This is unsurprising, since the survival benefits of receiving RT and CT have been described in many previous studies.^{3,8,18,22} Bhimani et al even explained why there was insufficient data to clarify the relationship between CT and survival in germ cell tumor patients in past decades.³² Still, the authors were able to conclude that suprasellar germinomas would benefit from CT. The effect of patient age or concurrent therapies may lead to these outcomes.

Our study did not reveal a significant survival difference between suprasellar and pineal germinomas. This can be explained by the fact that both the pineal region and suprasellar region are located in midline structures, which are typical sites for germinomas, and share similar therapeutic regimens. Earlier studies found differences in the prognosis of germinomas arising from different intracranial sites, with patients suffering from germinomas in typical sites having a relatively more prolonged progression-free survival in comparison with atypical sites (including basal ganglia and the cerebral cortex, $P = .03$).³² A biological difference between germinomas at typical or atypical sites has not been discovered. However, this is not the main focus of this article. Moreover, our study suggested that larger tumors may be associated with poorer survival, but the difference was not statistically significant for this cohort. To our best knowledge, there are no reports on the relationship between the tumor size of iGCTs and the prognosis that could serve as a reference. According to the results of K-M curve analysis, we only may

speculate that early-stage patients with larger tumor size may have a poorer prognosis.

Some prior relevant studies with adequate sample size have studied intracranial germinoma diagnosis and outcomes to some extent.^{22,33-35} Our investigation had strengths. First, none of these studies have focused on epidemiology, management, and long-term survival outcomes of intracranial typical site germinomas that are a special category of intracranial germinoma.³ Therefore, it is necessary to launch a new study to exploit it. Second, we found pronounced epidemiological differences between pineal germinomas and suprasellar germinomas, which could facilitate early detection of pineal germinomas. Third, there was significant variation in the choice of treatment modalities for pineal germinomas and suprasellar germinomas, which do not lead to different clinical outcomes regarding overall survival. This is an interesting finding and deserves further exploration.

Limitations

Our work should be considered in the context of the inherent limitations of the SEER database when critically evaluating the abovementioned findings. The SEER database used in the study containing 18 cancer registries is potentially affected by some particular clinical centers, leading to further validation with patient data. Moreover, data collection and reporting to SEER by different contributors from different clinical centers can present a significant challenge for researchers in terms of accurately capturing and evaluating a specific patient population. Most importantly, there is no information on specific RT and CT regimens in the current SEER database and only de-identified data is available. The chemotherapy regimens applied, including pharmaceutical combinations, dosages, and cycle counts, as well as the dose and radiation field used, were all unknown.³⁶⁻³⁸ Furthermore, the SEER program did not include data on intraoperative findings, postoperative complications, and molecular diagnoses, as well as changes in endocrine responsiveness and tumor markers before and after therapy. It is regrettable that the treatment data was not sufficient for logistic regression or Cox regression analysis.

Conclusions

In this retrospective study, we attempted to provide more information on the differences in epidemiology, management patterns, and survival outcomes between suprasellar and pineal germinomas. We demonstrated a higher proportion of male patients and larger tumors among the pineal germinoma cases. The administration ratios of RT and CT were similar for the 2 groups, but suprasellar germinoma patients were more likely to undergo surgery. RT and CT were both associated with improved long-term overall survival, while surgery was not. And the tumor site did not affect survival outcomes. Additional research is required to corroborate our findings.

Authors' contributions

Methodology, C.W.; software, C.W.; validation, W.Y, Z. Y, L.J. and W.X.; formal analysis, C.W.; resources, C.W, W.Y.; writing-original draft preparation, C.W.; writing-review and editing, L.J.; supervision, W.X, L.J.; project administration, L.J. All authors have read and agreed to the published version of the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Availability of Data and Material

Data reported in this manuscript were collected from the SEER database. Copies of these data can be obtained free of charge from <https://seer.cancer.gov>.

Ethics approval

All patient data in NCI SEER is anonymized, and the study received a waiver for consent from the ethics committee due to its retrospective nature and guaranteed patient privacy.

Consent to participate

Not applicable as the SEER database was analyzed retrospectively.

Consent for publication

All of the authors consented to have their work published for free.

ORCID iDs

Xiangyu Wang  <https://orcid.org/0000-0001-5103-433X>

Jun Lyu  <https://orcid.org/0000-0002-2237-8771>

Supplemental material

Supplemental material for this article is available online.

References

1. Douglas-Akinwande AC, Mourad AA, Pradhan K, Hattab EM. Primary intracranial germinoma presenting as a central skull base lesion. *AJNR. American journal of neuroradiology*. 2006;27(2):270-273.
2. Jorsal T, Rørth M. Intracranial germ cell tumours. A review with special reference to endocrine manifestations. *Acta Oncol*. 2012; 51(1):3-9.
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(12):1565-1577.
4. Seregini E, Massimino M, Nerini Molteni S, et al. Serum and cerebrospinal fluid human chorionic gonadotropin (hCG) and alpha-fetoprotein (AFP) in intracranial germ cell tumors. *Int J Biol Markers*. 2002;17(2):112-118.
5. Fujimaki T. Central nervous system germ cell tumors: Classification, clinical features, and treatment with a historical overview. *J Child Neurol*. 2009;24(11):1439-1445.
6. Weksberg DC, Shibamoto Y, Paulino AC. Bifocal intracranial germinoma: a retrospective analysis of treatment outcomes in 20 patients and review of the literature. *Int J Radiat Oncol Biol Phys*. 2012;82(4):1341-1351.
7. Brandes AA, Pasetto LM, Monfardini S. The treatment of cranial germ cell tumours. *Cancer Treat Rev*. 2000;26(4):233-242.
8. Takami H, Graffeo CS, Perry A, Giannini C, Daniels DJ. *Epidemiology, Natural History, and Optimal Management of Neurohypophyseal Germ Cell Tumors*; 2020:1-9.
9. Bamberg M, Kortmann R-D, Calaminus G, et al. Radiation therapy for intracranial germinoma: results of the german cooperative prospective trials MAKEI 83/86/89. *J Clin Oncol*. 1999;17(8):2585-2585. MAKEI 83/86/89.
10. Haddock MG, Schild SE, Scheithauer BW, Schomberg PJ. Radiation therapy for histologically confirmed primary central nervous system germinoma. *Int J Radiat Oncol Biol Phys*. 1997; 38(5):915-923.
11. 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(12):1661-1672.
12. Scherz A, Feller K, Berezowska S, Genitsch V, Zweifel M. Successful treatment of pituitary germinoma with etoposide, cisplatin, vincristine, methotrexate and bleomycin chemotherapy without radiotherapy. *Anticancer Res*. 2017;37(6):3111-3115.
13. Fu H, Guo X, Li R, Xing B. Radiotherapy and chemotherapy plus radiation in the treatment of patients with pure intracranial germinoma: A meta-analysis. *J Clin Neurosci*. 2017;43:32-38.
14. Yang J, Li Y, Liu Q, et al. Brief introduction of medical database and data mining technology in big data era. *J Evid Base Med* 2020;13(1):57-69.
15. Wu W-T, Li Y-J, Feng A-Z, et al.. Data mining in clinical big data: The frequently used databases, steps, and methodological models. *Mil Med Res* 2021;8(1):1-12.
16. Poynter JN, Fonstad R, Tolar J, Spector LG, Ross JA. Incidence of intracranial germ cell tumors by race in the United States, 1992-2010. *Journal of neuro-oncology*. 2014;120(2):381-388.
17. Makino K, Nakamura H, Yano S, Kuratsu J-I, neurosurgery KBTRGJP. Incidence of primary central nervous system germ cell tumors in childhood: a regional survey in Kumamoto prefecture in southern Japan. *Pediatr Neurosurg*. 2013;49(3):155-158.
18. Takami H, Graffeo CS, Perry A, Giannini C, Daniels DJ. Epidemiology, natural history, and optimal management of neurohypophyseal germ cell tumors. *J Neurosurg*. 2020;1(aop):1-9.
19. Willis RAJTboe, pathology. *The Borderland of Embryology and Pathology*; 1958.

20. Nichols CR, Fox EP. Extragonadal and pediatric germ cell tumors. *Hematol Oncol Clin N Am*. 1991;5(6):1189-1209.
21. Luna MA, Valenzuela-Tamariz J, Valenzuela-Tamariz JJAjocp. Germ-cell tumors of the mediastinum, postmortem findings. *Am J Clin Pathol*. 1976;65(4):450-454.
22. Bhimani AD, Barrington NM, Aguilar TM, Arnone GD, Mehta AI. Pituitary germinomas: a multi-institutional study analyzing patient demographics and management patterns. *Pituitary*. 2020; 23(4):381-388.
23. Lo AC, Hodgson D, Dang J, et al. Intracranial germ cell tumors in adolescents and young adults: A 40-year multi-institutional review of outcomes. *Int J Radiat Oncol Biol Phys*. 2020;106(2): 269-278.
24. Duffner PK. Long-term effects of radiation therapy on cognitive and endocrine function in children with leukemia and brain tumors. *Neurol*. 2004;10(6):293-310.
25. Khatua S, Fangusaro J, Dhall G, Boyett J, Wu S. , Bartels UJN-O. GC-17THE children's oncology group (COG) current treatment approach for children with newly diagnosed central nervous system (CNS) localized germinoma (ACNS1123 STRATUM 2). *Neuro-Oncology* 2016;18(suppl 3):iii45.
26. Sethi RV, Marino R, Niemierko A, Tarbell NJ, Yock TI, MacDonald SM. Delayed diagnosis in children with intracranial germ cell tumors. *J Pediatr*. 2013;163(5):1448-1453.
27. Millard NE, Dunkel IJ. Advances in the management of central nervous system germ cell tumors. *Curr Oncol Rep*. 2014;16(7):393.
28. Sawamura Y, Ikeda J, Shirato H, Tada M, Abe H. Germ cell tumours of the central nervous system: treatment consideration based on 111 cases and their long-term clinical outcomes. *Eur J Cancer*. 1998;34(1):104-110.
29. Matsutani M, Sano K, Takakura K, et al. Primary intracranial germ cell tumors: a clinical analysis of 153 histologically verified cases. *J Neurosurg*. 1997;86(3):446-455.
30. 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(22):2464-2471.
31. Frappaz D, Conter CF, Szathmari A, Valsijevic A, Mottolese C. The management of pineal tumors as a model for a multidisciplinary approach in neuro-oncology. *Neurochirurgie*. 2015; 61(2-3):208-211.
32. Packer RJ, Cohen BH, Cooney K. Intracranial germ cell tumors. *Oncol*. 2000;5(4):312-320.
33. Denyer S, Bhimani AD, Patil SN, Mudreac A, Behbahani M, Mehta AI. Treatment and survival of primary intracranial germ cell tumors: a population-based study using SEER database. *J Cancer Res Clin Oncol*. 2020;146(3):671-685.
34. Wang WG, Ye H, Chinnaiyan P. Practice patterns and survival outcomes of intracranial germinoma: an analysis of the National Cancer Database. *J Neuro Oncol*. 2018;137(1):77-82.
35. McCarthy BJ, Shibui S, Kayama T, et al. Primary CNS germ cell tumors in Japan and the United States: an analysis of 4 tumor registries. *Neuro Oncol*. 2012;14(9):1194-1200.
36. Morton LM, Dores GM, Schonfeld SJ, et al. Association of chemotherapy for solid tumors with development of therapy-related myelodysplastic syndrome or acute myeloid leukemia in the modern era. *JAMA Oncol*. 2019;5(3): 318-325.
37. Youn P, Li H, Milano MT, Stovall M, Constine LS, Travis LB. Long-term survival among Hodgkin's lymphoma patients with gastrointestinal cancer: a population-based study. *Ann Oncol*. 2013;24(1):202-208.
38. Williams SB, Shan Y, Jazzar U, et al. Comparing survival outcomes and costs associated with radical cystectomy and trimodal therapy for older adults with muscle-invasive bladder cancer. *JAMA Surgery*. 2018;153(10):881-889.