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Long-term outcomes and late complications of intracranial germinoma: Implications for follow-up policy

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Abstract

Background. We retrospectively assessed the long-term efficacy, safety, and functional outcome of chemotherapy and radiotherapy (RT) in patients with intracranial germinoma (iGE).

Methods. A total of 160 patients with iGE treated between 1983 and 2013 were reviewed. Overall survival (OS) was estimated using Kaplan-Meier method. The cumulative incidence of recurrence (CIR), and secondary malignancies (CISM) were analyzed using cumulative incidence functions (CIFs), with death without the event of interest treated as a competing risk. Functional outcomes were assessed using the Karnofsky Performance Scale (KPS). Cox proportional hazards regression was used to analyze predictive factors.

Results. The mean follow-up duration was 157.1 months. The 5-/10-year OS rates were 93.8% and 88.6%. The 5- and 10-year CIRs were both 5.6%, whereas the CISM were 0.6% and 2.1%, respectively. Secondary malignancies developed in 14 patients, most commonly glioblastoma. Thirty-one patients died from disease-, treatment-, or secondary malignancy-related causes. Additional causes of death were identified during long-term follow-up, even more than 20 years after treatment. Functional outcomes remained favorable (KPS $\geq$ 60) in 90.6% at 5 years and 88.5% at 10 years. Chemotherapy combined with reduced extent and reduced-dose RT significantly improved OS without increasing the CIR.

Conclusions. Despite the generally favorable prognosis, secondary malignancies and disease- and treatment-related long-term adverse effects significantly affect patient outcomes in iGE. Long-term follow-up (over 20 years) is essential for detecting and managing these complications. Chemotherapy with reduced-extent and reduced-dose RT may help minimize long-term adverse effects.

Key Points

- 10-year OS, CIR, and CISM rates for iGE were 88.6%, 5.6%, and 2.1%, respectively.
- Long-term follow-up is crucial to detect late complications and secondary malignancy.
- Chemotherapy with reduced radiotherapy improves OS and functional outcomes.

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Importance of the Study

This retrospective study on iGE investigated long-term outcomes and treatment strategies. Notably, the 5- and 10-year OS rates were high, whereas CIR and CISM were low. Furthermore, the results of this study underscore the importance of reducing the extent and dose of radiotherapy in combination with adjuvant chemotherapy to optimize patient outcomes. It provides detailed data on secondary malignancies and long-term adverse effects for patients with iGE, especially those who underwent treatment more than a decade ago, revealing a late hazard phase beyond 20 years that has often been overlooked in previous studies. This research highlights the necessity of vigilant, long-term follow-up and supports the development of personalized, less toxic treatment regimens. Ultimately, it improves the quality of care for patients with iGE and offers a roadmap for future studies in the field of pediatric neuro-oncology.

Intracranial germ cell tumors account for approximately 3% of all primary brain tumors worldwide,[1–3] and in Korea they represent up to 11.2% of pathologically confirmed pediatric brain tumors.[4] Among these, intracranial germinoma (iGE) is the most common subtype and is predominantly diagnosed in children and young adults. The standard treatment for iGE comprises a combination of surgery, chemotherapy, and radiotherapy (RT). Long-term outcomes in iGE depend on factors such as patient age, general health status, tumor size and location, and treatment responsiveness.

The prognosis of iGE is generally favorable, with 5- and 10-year overall survival (OS) rates near 90%, and recurrence-free survival rates of approximately 80% in previous studies.[5] Despite these encouraging survival outcomes, long-term complications remain a significant concern. In particular, the risk of secondary malignancies is elevated in patients with cranial irradiation, especially those treated at a young age.[6,7] These secondary malignancies may occur many years after initial treatment and can substantially impact both OS and quality of life.[8] In addition to secondary malignancies, various risk factors contribute to disease- and treatment-related long-term complications, including long-term sequelae of chemotherapy and RT.[9,10]

In this study, we assessed OS, cumulative incidence of recurrence (CIR), and cumulative incidence of secondary malignancy (CISM), along with functional outcomes, and investigated the causes of functional decline and death.

Methods

Data Collection and Variables

In this retrospective study, we analyzed patients treated at our institutions between March 1983 and December 2013. We included patients who were diagnosed with iGE based on histopathological confirmation via biopsy or whose diagnosis was supported by radiological findings suggestive of iGE and serum levels of alpha-fetoprotein less than 10 ng/mL and β-human chorionic gonadotropin (β-HCG) less than 100 mIU/MI.[11] Patients were excluded if they refused treatment, had less than 5 years of follow-up without justifiable causes such as death, or if patient information was unavailable. By analyzing the selected patient population based on these criteria, we aimed to better understand clinical features focusing on the long-term outcomes of this patient group.

Data on age, sex, tumor location, tumor markers, histologic findings, metastasis status, radiological findings, chemotherapy or RT protocols administered, and treatment outcomes were collected from a clinical data repository system. Metastasis was defined as either abnormal cerebrospinal fluid cytology or evidence of tumor presence in the brain or spinal cord on magnetic resonance imaging (MRI). Treatment outcomes were evaluated in terms of OS, CIR, CISM, and functional status. The functional outcome was evaluated using the Karnofsky Performance Scale (KPS) score. An unfavorable outcome was defined as a KPS score less than 60 (<60). Tumor recurrence was determined by MRI. Follow-up MRI scans were scheduled every 6 months during the first 5 years after initial diagnosis, then annually for years 6 through 10, and thereafter only when there was clinical suspicion of recurrence or progression. During these visits, patients also underwent systematic clinical assessments, including detailed history taking and physical examinations, to identify potential treatment-related morbidities such as endocrine abnormalities, neurological deficits, psychiatric symptoms, and other long-term complications. Secondary malignancies were defined as tumors that occurred within the previous irradiation field, were absent before the initial treatment, had different histological features from the primary tumor, and emerged after an appropriate latent period—at least 5 years for solid tumors and at least 2 years for hematologic malignancies.[12] For analysis, the extent and dose of RT were classified based on the combined data from conventional RT and proton beam therapy. The extent of RT was categorized into 4 groups: craniospinal irradiation (CSI), whole-brain (WB), whole-ventricle (WV), and involved-field RT (IFRT). Each group includes patients who received the corresponding treatment alone or in combination with additional RT to the same extent; for example, the WB group includes WBRT only and WBRT+IFRT.

This study protocol was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. 2304-076-1422) and was conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived by the IRB.

Statistical Analysis

Categorical variables are summarized as frequencies and percentages, while continuous variables are reported as means ± standard deviations. Univariate and multivariate analyses were conducted using Cox proportional hazards models to compare outcomes among treatment combinations of surgery, chemotherapy, and RT. OS was defined as the interval from diagnosis to death from any cause or last follow-up. CIR and CISM were estimated using cumulative incidence functions (CIF), with death without the event of interest treated as a competing risk. Group differences in CIF were assessed using Gray's test. OS and functional outcomes were estimated using the Kaplan-Meier method. Statistical analyses were performed using R software (version 4.4.1; R Foundation for Statistical Computing, Vienna, Austria), and a $P < .05$ was considered statistically significant.

Results

Patient Characteristics

Among the 193 patients diagnosed with iGE, 31 were excluded because of inadequate follow-up (<5 years) without justifiable causes, and 2 declined treatment. Ultimately, 160 patients were enrolled, of whom 153 (95.6%) had a pathologically confirmed diagnosis by biopsy and 7 (4.4%) were diagnosed based on characteristic radiological findings together with tumor markers. The mean age at diagnosis was 15.6 years (range: 3-44; males: 16.4; females: 12.8). A total of 124 patients (77.5%) were male, a significantly greater proportion than female. The tumor locations were as follows: pineal region in 59 patients (36.9%), suprasellar region in 51 (31.9%), bifocal involvement of both suprasellar and pineal regions in 17 (10.6%), basal ganglia (BG)-thalamus region in 29 (18.1%), midbrain tecum in 2 (1.3%), and frontal lobe in 2 (1.3%). Serum β-hCG was ≤3 mIU/mL in 113 patients (70.6%) and ranged from >3 to 100 mIU/mL (mean 9.0 mIU/mL) in 44 patients (27.5%); data were unavailable for 3 patients. CSF β-hCG was ≤ 3 mIU/mL in 45 patients (28.1%) and ranged from >3 to 898 mIU/mL (mean 74.1 mIU/mL) in 68 patients (42.5%); data were unavailable for 47 patients. Among the 153 patients who underwent surgical biopsy or resection, 144 were confirmed to have a pure germinoma, and 9 had a germinoma with a mature teratoma component; in those 9 patients, no additional complications affecting survival or functional outcomes were noted after surgical resection. Metastasis was detected by cerebrospinal fluid analysis or MRI in 18.7% of patients, whereas the majority presented with localized tumors at the initial evaluation. The mean follow-up duration was 157.1 months (Supplementary Table S1).

Preoperative Symptoms

The most common presenting symptoms were headache (40.6%) and nausea/vomiting (27.5%). Diplopia (30.6%) was frequently observed in pineal lesions, whereas polyuria and polydipsia (23.1%) were more common in suprasellar lesions. Lesions involving the BG-thalamus regions were often associated with weakness (11.9%), dystonia (2.5%), and sensory changes (0.6%). Additional presentations included dizziness (3.8%), memory impairment (1.9%), and seizures (1.9%) (Supplementary Table S2).

Treatment

Hydrocephalus was identified at diagnosis in 72 patients (45.0%). Among them, 35 (48.6%) underwent endoscopic third ventriculostomy, 16 (22.2%) received ventriculoperitoneal shunting, and 21 (29.2%) experienced spontaneous resolution of hydrocephalus (Supplementary Table S1). Records related to hydrocephalus were unavailable for 4 patients.

Following diagnosis, patients received chemotherapy and/or RT (Supplementary Table S3). Chemotherapy was administered to 122 patients (76.3%), whereas 37 (23.1%) did not receive it, and data regarding chemotherapy administration were unavailable for 1 patient. A total of 157 patients (98.1%) underwent RT. In 8 patients, including 4 who received proton beam therapy, the exact extent or dose of radiation was not documented. Three patients did not undergo RT: one declined treatment, and 2 were deemed medically unfit because of unstable vital signs. The mean radiation doses administered were 25.7 Gy to the craniospinal axis, 37.6 Gy to the whole brain, 21.4 Gy to the whole ventricle, and 40.4 Gy to the involved field. The extent and dose of radiation differed significantly depending on whether chemotherapy was administered (Supplementary Table S4). Patients who received chemotherapy were given a mean dose of 45.9±8.7 Gy, while those who did not receive chemotherapy were treated with a higher mean dose of 52.1±9.8 Gy ($P<.001$) at the primary tumor. Slight variations in treatment protocols occurred over the long study period, resulting in differences in chemotherapy regimens and in the extent and dose of RT among individual patients (Supplementary Table S5 and Supplementary Figure S1). Since the 2000s, the adoption of chemotherapy has become more widespread, allowing a reduction in both the extent of RT and the dose of radiation to the primary site, and this trend was observed regardless of metastatic status (Supplementary Figure S2).

Long-term Complications after Treatment

Following treatment, 31 patients (19.5%) required at least one hormone replacement therapy. Seven patients (4.4%) developed new posttreatment motor deficits, while one patient (0.6%) experienced sensory changes. Eight patients (5.0%) experienced psychiatric problems necessitating treatment, primarily with depression, avolition, and anhedonia; among these, 3 were diagnosed with intellectual impairment, and one was diagnosed with schizophrenia. Visual complications, including blurred vision, visual acuity decline, or visual field defects, were observed in 7 patients (4.4%). Four patients (2.5%) developed radiation-induced vasculopathy: 3 were diagnosed with radiation-induced

Table 1. Long-term complications after treatment

Complications	All	CTx (+) (*N*=122)	CTx (–) (*N*=37)	*P*
Overall long-term complications	42 (26.4%)	25 (20.5%)	17 (45.9%)	.004
Endocrine/electrolyte abnormality	31 (19.5%)	17 (13.9%)	14 (37.8%)	.003
Motor weakness	7 (4.4%)	3 (2.5%)	4 (10.8%)	.087
Psychiatric problem	8 (5.0%)	6 (4.9%)	2 (5.4%)	1.000
Impaired vision	7 (4.4%)	5 (4.1%)	2 (5.4%)	1.000
Vasculopathy	4 (2.5%)	1 (0.8%)	3 (8.1%)	.060
Sensory change	1 (0.6%)	0 (0%)	1 (2.7%)	.526

Abbreviation: CTx: chemotherapy.

moyamoya syndrome and underwent encephaloduroarteriosynangiosis, and one experienced symptomatic cerebral infarction. Fifteen patients exhibited multiple complications involving 2 or more categories. Compared with the non-chemotherapy group (45.9%, 17 of 37), the group that received adjuvant chemotherapy combined with reduced-extent and reduced-dose RT had a significantly lower overall long-term complication rate (20.5%, 25 of 122) (*P*=.004) (Table 1).

Survival and Functional Outcomes

The 5- and 10-year OS rates were 93.8% (95% CI: 90.1%-97.6%) and 88.6% (95% CI: 83.7%-93.9%), respectively (Supplementary Figure S3A). The CIR at both 5 and 10 years were 5.6% (95% CI: 2.0%-9.2%) (Supplementary Figure S3B). The CISM were 0.6% (95% CI: 0.0%-1.9%) at 5 years and 2.1% (95% CI: 0.0%-4.4%) at 10 years (Supplementary Figure S3C). The OS rates declined late, after approximately 20 years. In contrast, the CIR plateaued after 5 years, whereas the CISM continued to increase over time.

Among the 31 patients who died after treatment, 9 (29%) succumbed to radiation-induced malignancies, including glioblastoma (GBL) (*N*=6), high-grade astrocytoma with piloid features (N=1), anaplastic astrocytoma without genetic testing (*N*=1), and medulloblastoma (*N*=1). Seven deaths (22.6%) were disease-related. Causes included central pontine myelinolysis secondary to acute electrolyte imbalance (*N*=1), relapse with chemotherapy resistance (*N*=2), acute hydrocephalus due to recurrence (*N*=1), deterioration of general condition during RT (*N*=2), and aspiration pneumonia during hospice care (*N*=1). Two patients (6%) died from treatment-related causes; one from shunt infection and another from bleomycin-induced interstitial pneumonitis. Four (13%) deaths resulted from accidents or self-harm, including one fall with head trauma of indeterminate intent and three suicide cases. Among the suicide cases, one occurred following a radiation-induced GBL diagnosis, while 2 exhibited posttreatment psychotic symptoms, with one having a prior schizophrenia diagnosis. The cause of death was undetermined in 9 patients (29%). Two were receiving hormone therapy and likely died because of inadequate medical follow-up after the loss of familial support stemming from financial hardship and parental separation. The remaining 7 patients were confirmed to have died, but no specific cause was identified (Table 2).

The group receiving adjuvant chemotherapy combined with reduced-extent and reduced-dose RT exhibited a statistically significant improvement in OS (*P*=.025), whereas the CIR did not show a corresponding increase. The CISM showed a trend similar to that of OS but did not reach statistical significance, likely because of the small number of patients (Figure 1A-C). The extent of RT did not significantly impact OS or CISM; however, the subgroup treated with IFRT only had a significantly higher recurrence rate (Figure 2A-C).

Fourteen patients developed secondary malignancies (Table 3). The most common diagnosis was GBL (*N*=6), followed by meningioma (*N*=3), astrocytic glioma (*N*=2: one high-grade astrocytoma with piloid features and one anaplastic astrocytoma according to the WHO 2005 brain tumor classification, at a time when genetic profiling was not available), basal cell carcinoma (*N*=1), medulloblastoma (*N*=1), and acute myeloid leukemia (AML) (*N*=1). Among these 14 patients, 11 were in their teens at the time of RT; the mean latency to diagnosis of secondary malignancies was 17.6 years. Eight patients had received CSI with IFRT, with a dose of 36 Gy to the whole brain and 24 Gy to the whole spine (range, 13.2-30 Gy). The median dose to the primary tumor was 55.8 Gy (range, 50.4-55.8 Gy). Two patients received WBRT with IFRT at 36 Gy to the whole brain; their primary tumor doses were 54 and 55.8 Gy, respectively. Additional 2 patients received WVRT with IFRT at 25.2 and 23.4 Gy to the whole ventricle; their primary tumor doses were 54 and 45 Gy, respectively. The remaining 2 patients underwent RT at a hospital outside our network, and although treatment records were available, the specific details were not.

Following treatment, the percentage of patients who maintained a KPS score ≥ 60 was 90.6% (95% CI: 86.2%-95.2%) at 5 years and 88.5% (95% CI: 83.6%-93.6%) at 10 years (Supplementary Figure S4). At the 10-year time point, the functional status of adjuvant chemotherapy subgroup was superior: 90.6% (95% CI: 85.6%-96.1%) maintained a KPS score ≥ 60, compared with 80.8% (95% CI: 68.9%-94.7%) in the non-chemotherapy group (*P*=.025; Figure 3A). However, when patients who died were excluded from the analysis, the association between chemotherapy use and preservation of functional status was attenuated and no longer statistically significant, suggesting that the observed relationship may partly reflect survival differences when death was included as part of the composite functional outcome (Supplementary Figure S5A). The extent of radiation did not significantly affect functional outcomes. Patients

Table 2. Comparison of characteristics and treatment methods between deceased and surviving patients

	Dead (n=31)	Alive (n=129)	P
Age of death (year), mean (SD)	28.0 (±11.0)		
Sex			.236
M	27 (87%)	97 (75.2%)	
F	4 (13%)	32 (24.8%)	
Tumor location			.793
Pineal	11 (36%)	48 (38.4%)	
Suprasellar	9 (29%)	42 (33.6%)	
Bifocal	4 (13%)	13 (10.4%)	
Basal ganglia-thalamus	7 (22%)	22 (17.6%)	
Other*	0 (0%)	4 (3.1%)	
Chemotherapy			<.01
Yes	14 (45%)	108 (84.4%)	
No	17 (55%)	20 (15.6%)	
RT**			.354
CSI	16 (52%)	57 (44.2%)	
WB	4 (14%)	9 (7.0%)	
WV	6 (19%)	43 (33.3%)	
IFRT	2 (6%)	12 (9.3%)	
N/A RT extent and dose data	1 (3%)	7 (5.4%)	
No RT	2 (6%)	1 (0.8%)	
Cause of death			
Secondary malignancy	9 (29%)		
Disease-related	7 (23%)		
Treatment-related	2 (6%)		
Other cause***	4 (13%)		
Unknown cause	9 (29%)		

Abbreviations: CSI, craniospinal irradiation; IFRT, involved-field radiotherapy; N/A, not available; RT, radiotherapy; WB, whole brain; WV, whole ventricle.
*Frontal lobe (1 case), tectum of midbrain (2 cases).
**Information on RT extent by group is presented in the table.
***Accidents or self-harm.

treated with IFRT maintained KPS score ≥ 60 in 85.7% (95% CI: 69.2%-100%). Those who received WVRT achieved KPS score ≥ 60 in 92.6% (95% CI: 84.7%-100%), and those who underwent WBRT in 84.6% (95% CI: 67.1%-100%). Patients who underwent CSI maintained KPS score ≥ 60 in 88.9% (95% CI: 81%-96.5%) (Figure 3B).

In the cohort, 4 patients had KPS < 60 prior to treatment, and an additional 24 patients experienced a decline in the KPS score to < 60 following therapy (Supplementary Table S6). This subgroup comprised 19 males and 5 females. Lesion distribution included 8 suprasellar, 8 pineal, 4 bifocal, and 4 BG cases. Twelve of these patients (50%) received chemotherapy. Regarding RT, 13 patients underwent CSI (mostly combined with IFRT), 3 received WBRT, 4 underwent WVRT with IFRT, and 2 received IFRT only. One patient received proton beam therapy at an external institution; detailed dose and field data were unavailable. The mean time to decline to a KPS score < 60 was 121 months overall and 58 months when cases of secondary malignancy were excluded. Most of the functional declines were associated with subsequent secondary malignancies. Among the 24 patients, 7 reported general weakness, one experienced a recurrent seizure, one had functional decline posttrauma, one had tumor recurrence, 6 developed limb paralysis requiring gait assistance or becoming bedridden, 6 required hospitalization or long-term nursing care for endocrine/electrolyte dysregulation (including 2 with central pontine myelinolysis), 4 developed infections (meningitis or pneumonia), 4 had visual impairment/disturbance necessitating daily-life assistance, 2 suffered cerebrovascular events (infarction or hemorrhage), 2 required psychiatric hospitalization for depression or hallucination, and in 2 patients, the cause was undetermined. Problems related to endocrine/electrolyte abnormalities or infections tended to appear relatively early, while other issues appeared at various times. Visual impairment can occur early or even after nearly 10 years. Among the 24 patients whose KPS scores fell below 60, 18 died.

Prognostic Factors

In the multivariate analysis for OS, bifocal tumor location showed a trend toward poorer outcome, whereas chemotherapy was significantly associated with improved survival. Age, sex, type of surgery, radiation extent, and metastatic status were not significantly associated with OS (Supplementary Figure S6A). For the CIR, tumors in the suprasellar region had a lower recurrence rate than those in other locations. Patients who did not undergo surgery also showed a lower hazard of recurrence. Conversely, compared with patients who received CSI, patients who received WVRT or IFRT had a higher hazard ratio for recurrence, whereas WBRT was associated with a lower hazard ratio (Supplementary Figure S6B). Regarding CISM, pineal tumor location was significantly associated with an increased risk of secondary malignancies, whereas tumors in the BG-thalamus location, chemotherapy, IFRT, and metastasis (M+) were associated with lower hazard ratios (Supplementary Figure S6C). Notably, the extent and dose of RT were not greater in pineal cases. However, for CIR, the effects of tumor location, surgery, and RT, as well as for CISM, the effects of BG-thalamus location, IFRT, and M stage, showed extremely large or small subdistribution hazard ratio (SHR) estimates, suggesting potential instability of these estimates. With respect to functional outcome, the administration of chemotherapy emerged as a favorable independent factor (Supplementary Figure S6D).

Discussion

Long-Term Complications and Survivor Care in iGE Patients

We conducted a comprehensive analysis of long-term outcomes and prognostic factors in a cohort of 160 patients with iGE. Although the prognosis of iGE is generally favorable, our findings highlight the potential for serious

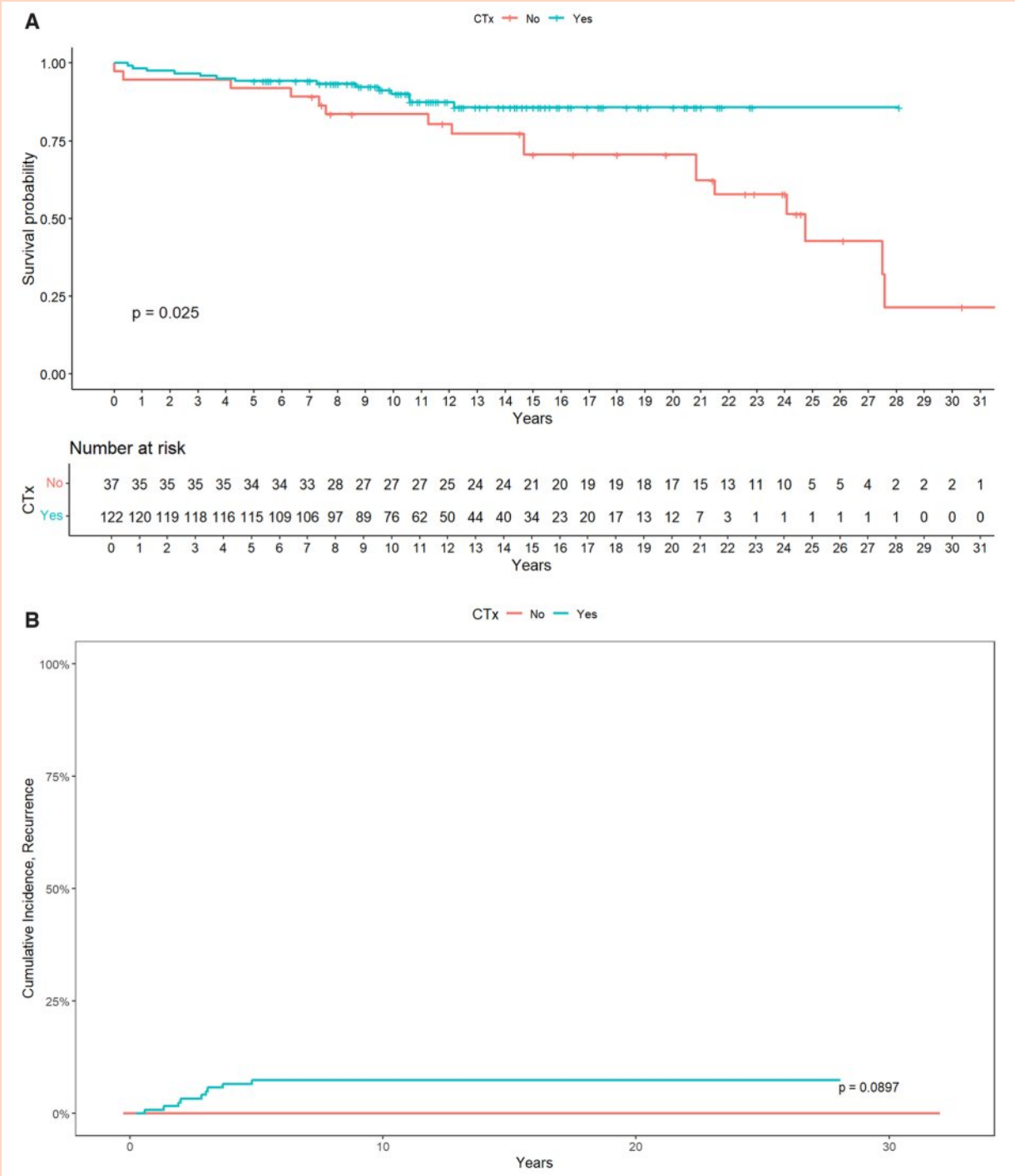

Figure 1. Overall survival (OS, A), cumulative incidence of recurrence (CIR, B), and cumulative incidence of secondary malignancy (CISM, C) according to chemotherapy. OS was estimated using the Kaplan-Meier method, while CIR and CISM were analyzed using cumulative incidence functions (CIF) to account for death without the event of interest as a competing risk. Group differences in CIF were assessed using Gray's test. Chemotherapy was associated with improved OS, whereas differences in CIR or CISM were not statistically significant. CTx: chemotherapy.

long-term complications. These include endocrine/electrolyte abnormalities, radiation-induced secondary malignancy, newly acquired neurological deficits (such as motor weakness, visual impairment, and sensory change), psychiatric disorders, and radiation-induced vasculopathy.

The most frequent complication was endocrine/electrolyte abnormalities. Given that germinomas commonly arise in the suprasellar and pineal regions which are closely associated with the hypothalamic-pituitary axis, RT may damage the gland and precipitate hormonal and electrolyte

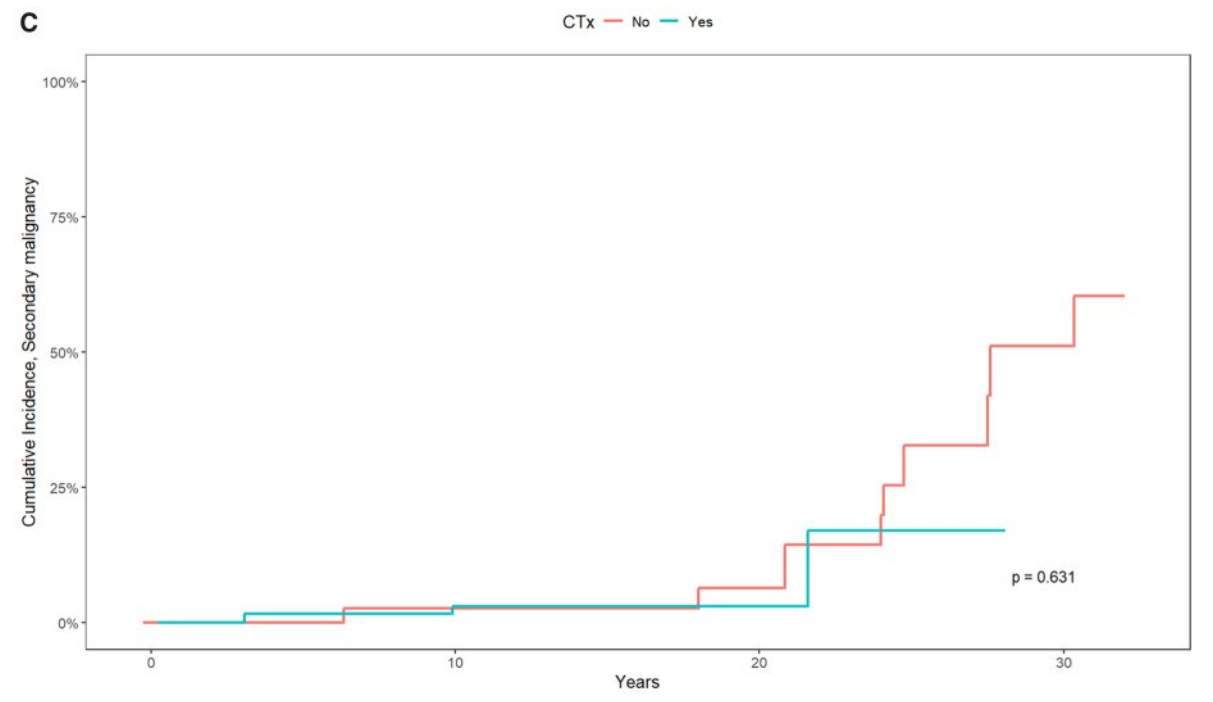

Figure 1. Continued.

disturbances. Sugiyama et al reported that in patients with iGE, 75% of deaths were attributed to hormonal catastrophes resulting from inadequate hormone replacement.[13] These findings underscore the need for rigorous endocrinology follow-up, especially in pediatric patients, to ensure appropriate hormone replacement and support normal growth and development.

Neurological deficits reflect the potential impact of both disease and treatment on functional ability and quality of life. These deficits may result from tumor location or growth, treatment-related effects, or radiation-induced vascular injury. The psychiatric complications observed in our cohort, including suicide, further underscore the importance of individualized survivor care. These findings are consistent with previous reports indicating that a significant proportion of patients experience mental health challenges.[8,14,15] Psychiatric symptoms may result from endocrine disturbances. For instance, hypercortisolism may lead to depression, cognitive impairment, delirium, and psychosis, whereas hypocortisolism may similarly manifest as depression, cognitive impairment, or delirium. Hyperthyroidism is associated with nervousness, emotional lability, and hyperkinesia, whereas hypothyroidism may present with depressive symptoms. Psychiatric disturbances, including psychosis, have also been observed in patients with diabetes insipidus and hypernatremia.[16]

Mortality in our cohort was attributable to factors such as secondary malignancy and tumor recurrence. Although our 5-year and 10-year OS rates are comparable with those reported in recent reports,[17–19] our extended follow-up revealed persistent late risks. These findings reaffirm the need for survivor care extending well beyond a decade. In particular, patients historically treated with wide-extent, high-dose radiation require vigilant surveillance for more than 20 years to enable timely intervention and improve long-term quality of life.

RT in iGE: De-Intensification Strategies and Long-Term Risk Balancing

In the management of iGE, RT remains the cornerstone of treatment.[20,21] However, efforts to reduce the radiation extent and dose have been undertaken to mitigate the long-term adverse effects of RT.[22] High-dose, wide-extent cranial irradiation increases the risk of secondary malignancy. In contrast, the incorporation of chemotherapy allows an adaptive reduction in the extent and dose of RT by leveraging the tumor response to systemic therapy.

Several studies have proposed treatment strategies combining chemotherapy with a reduced extent/dose of RT. More recently, protocols employing WBRT or WVRT with chemotherapy have been reported as acceptable therapeutic options.[17,23–26] Nonetheless, as reported by Eom et al,[27] patients treated with reduced-extent RT exhibited high recurrence rates. Specifically, adjuvant chemotherapy followed by WVRT or IFRT with dose reduction did not achieve tumor control as reliably as CSI did. Therefore, caution is warranted when reducing the extent of RT, given the competing need to minimize late toxicity while maintaining disease control.

The occurrence of various tumor types—including meningiomas, sarcomas, and gliomas—has been reported after cranial irradiation.[6] In the present study, 14 patients developed secondary malignancies, with a mean latency

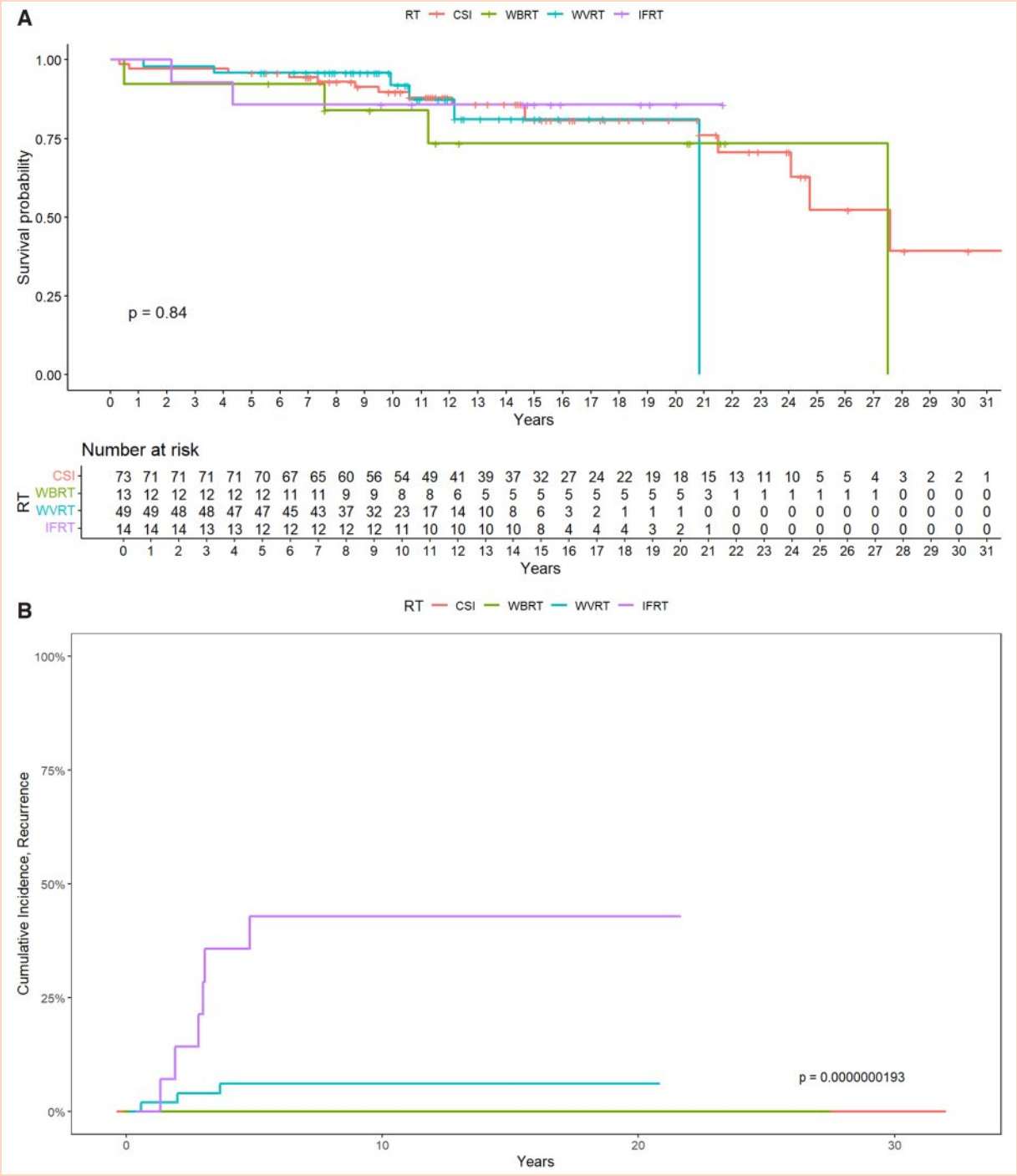

Figure 2. Overall survival (OS, A), cumulative incidence of recurrence (CIR, B), and cumulative incidence of secondary malignancy (CISM, C) according to the extent of radiation. IFRT was associated with worse CIR. RT: radiotherapy, CSI: craniospinal irradiation, WBRT: whole brain RT, WVRT: whole ventricle RT, IFRT: involved-field RT.

of 17.6 years. Among these patients, 12 (representing 7.6% of those who had undergone RT) developed intracranial secondary tumors. Previously reported incidence rates of second primary brain tumors following cranial irradiation for pituitary adenoma ranged from 1.2% to 2.4%, which were lower than those observed in our cohort.[27,28] The higher incidence in our study may reflect the longer follow-up period as well as the broader extent and higher doses of radiation administered. Consequently, numerous investigators have emphasized that the extent and dose of RT are critical factors of long-term toxicity. Strategies aimed at mitigating the late complications associated with extensive, high-dose irradiation have therefore been proposed for iGEs.[29–34] Nonetheless, the optimal extent and

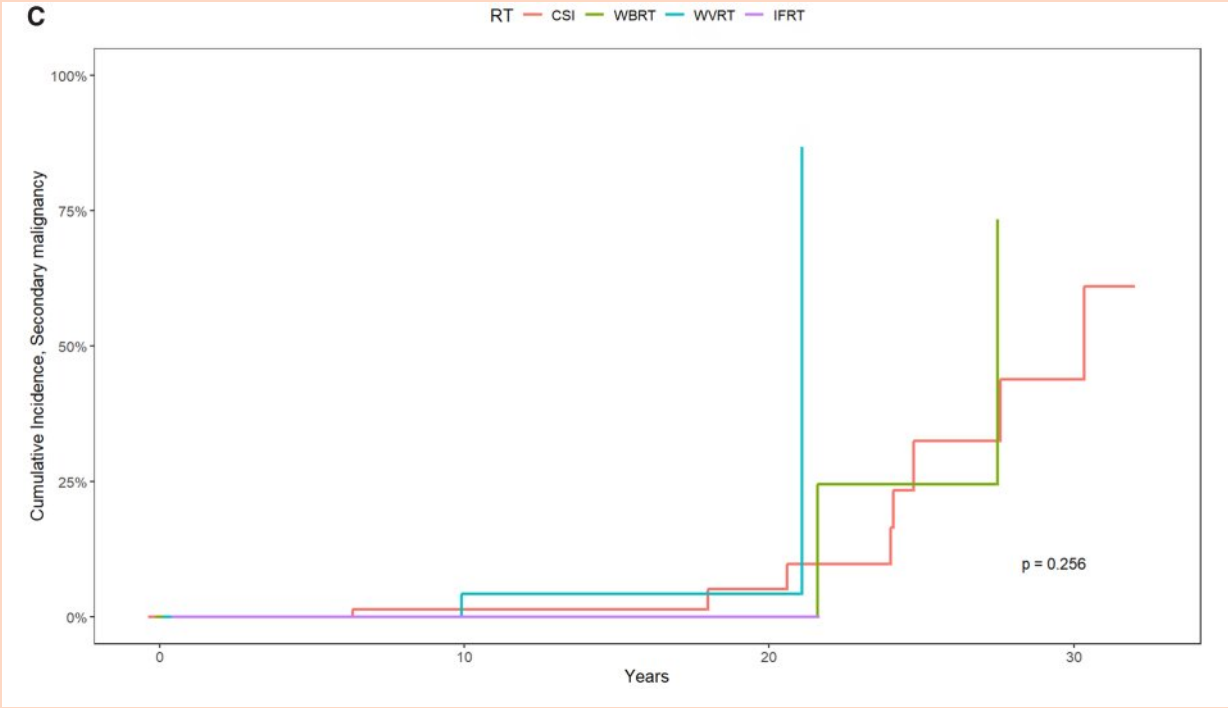

Figure 2. Continued.

dose of RT remain under debate. In our institutions, we gradually reduced the extent and dose of radiation over time in an effort to balance tumor control with long-term safety.

Chemotherapy-Enabled RT Deintensification: Long-Term Outcomes and Risk Considerations

In our study, patients who received chemotherapy had significantly improved OS and better preservation of KPS scores. We interpret this improvement not as a sole effect of chemotherapy itself but rather as a combined effect whereby chemotherapy enabled reductions in both the extent and dose of radiation, thereby contributing to improved survival and functional outcomes.

Notably, in the non-chemotherapy group, we observed a marked and continuous decline in OS and KPS scores, accompanied by a gradual increase in the CISM, although this increase did not reach statistical significance. In contrast, the CIR remained stable beyond 5 years after treatment in both groups. This pattern suggests that large-extent, high-dose RT may contribute to late adverse effects that negatively impact long-term survival and functional status even in the absence of tumor recurrence. Collectively, our findings support treatment strategies incorporating chemotherapy to enable radiation de-intensification in the management of iGE.

In our multivariable analysis, the use of chemotherapy remained significantly associated with improved functional outcomes, whereas RT was not. However, this finding should be interpreted with caution, as functional outcomes were assessed using KPS, which may not adequately capture subtle but clinically relevant neurocognitive impairments, including deficits in attention, executive function, memory, and processing speed. These domains are more appropriately evaluated through formal neuropsychological testing, which is essential for detecting treatment-related cognitive sequelae. Therefore, the absence of a significant association between RT parameters and functional outcomes may partly reflect limitations of the assessment tool rather than a true lack of effect. In this context, observed functional benefit in the chemotherapy (+RT) group cannot be fully explained by differences in RT parameters alone. Secondary malignancy, which accounted for a substantial proportion of long-term functional decline, is closely linked to cumulative radiation exposure, underscoring the continued importance of RT—particularly its extent and dose—in determining late outcomes. Because both RT extent and dose were modified concurrently during the chemotherapy era, their additive or synergistic effects may not be fully captured when analyzed separately. The chemotherapy (+RT) group also demonstrated better preservation of functional status, which may reflect reduced late toxicity, including secondary malignancy and other radiation-related complications. Given temporal changes in treatment strategies and supportive care, residual confounding cannot be excluded. It therefore remains uncertain whether contemporary RT-only strategies using reduced extent and dose would achieve outcomes comparable to those observed with combined chemotherapy and RT in our study.

In addition, one patient in our cohort developed AML 3 years after treatment, having received proton therapy and combination chemotherapy including carboplatin,

Table 3. Cases of secondary malignancy

Patient No.	Sex/Age*	Primary site	Type of primary surgery	Chemotherapy	RT extent	RT dose (Gy)	Secondary pathology	Site	Latent period** (years)	Survival
1	M/45	P	Tumor resection	No	CSI+IFRT	WB36+WS24, tumor dose 55.8	GBL	CbII	22	Death
2	M/39	SS	Open bx.	No	CSI+IFRT	WB36+WS24, tumor dose 55.8	GBL	Lt F-P-T lobe	26	Death
3	M/32	P	Tumor resection	No	CSI+IFRT	WB36+WS24, tumor dose 50.4	GBL	Lt BG, thalamus	19	Death
4	M/20	P, SS	Stereotactic bx.	No	CSI+IFRT	WB36+WS19.5, tumor dose 54	GBL	Brain stem	6	Death
5	M/34	P	Tumor resection	No	WV+IFRT	WV25.2, tumor dose 54	GBL	Rt BG, thalamus	18	Death
6	M/36	P	Tumor resection	No	WB+IFRT	WB36, tumor dose 55.8	GBL	Lt T-O lobe	25	Death
7	F/32	SS	Open bx.	No	CSI+IFRT	WB36+WS13.2, tumor dose 55.8	AA	Rt F-T lobe	22	Death
8	M/28	P	Tumor resection	No	CSI+IFRT	WB36+WS24, tumor dose 55.8	AA	Rt thalamus	14	Alive
9	F/36	SS	No surgery	No	CSI+IFRT	WB36+WS24, tumor dose 55.8	Atypical MNG	Lt F convexity	28	Alive
10	F/28	SS	Tumor resection	No	CSI+IFRT	WB36+WS30, tumor dose 55.8	MNG	Rt P convexity	19	Alive
11	M/37	P	Stereotactic bx.	CDDP/VP-16	No data	No data	MNG	Rt sphenoid ridge	16	Alive
12	M/48	P	Stereotactic bx.	CDDP/VP-16	WB+IFRT	WB36, tumor dose 54	Basal cell carcinoma	Scalp	20	Alive
13	M/24	P	Stereotactic bx.	8-in-1	WV+IFRT	WV23.4, tumor dose 45	Medulloblastoma	Lt CbII peduncle	9	Death
14	M/14	P	Tumor resection	BEP	No data	No data	AML	–	3	Death

*Age at diagnosis of secondary malignancy.
**The duration until the occurrence of the secondary malignancy.
Abbreviations: 8-in-1, solumedrol, vincristine, lomustine, procavazine, hydroxyurea, cisplatin, cytosine, arabinoside, and cyclophosphamide; AA, anaplastic astrocytoma; AML, acute myeloid leukemia; BEP, bleomycin, etoposide, cisplatin; BG, basal ganglia; bx, biopsy; CbII, cerebellum; CDDP/VP-16, cisplatin and etoposide; CSI, craniospinal irradiation; F, frontal; F-P-T, frontoparietotemporal; F-T, frontotemporal; GBL, glioblastoma; IFRT, involved-field radiotherapy; MNG, meningioma; P, parietal; P, pineal lesion; RT, radiotherapy; SS, suprasellar lesion; T-O, temporooccipital; WB, whole brain; WS, whole spine; WV, whole ventricle.

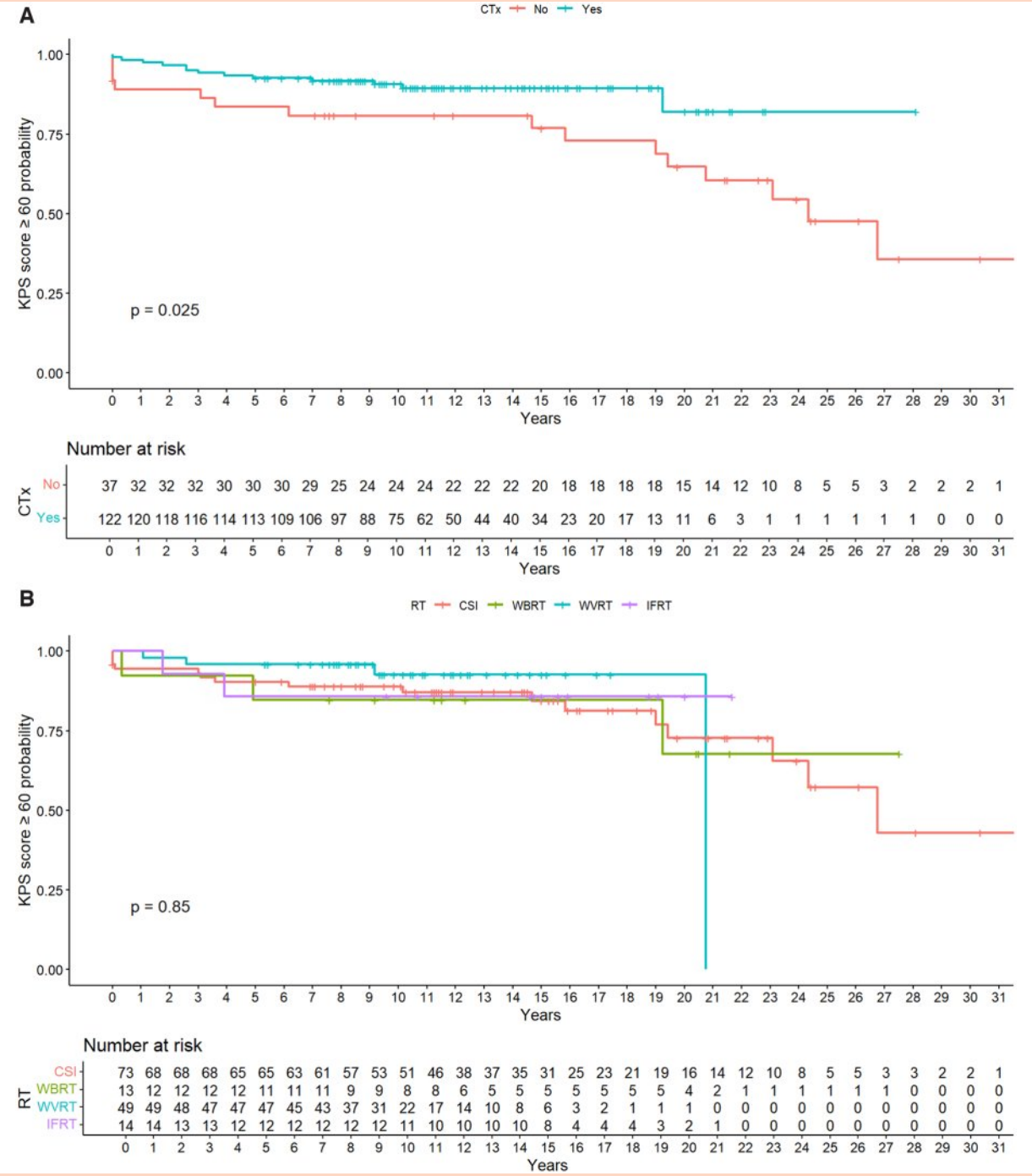

Figure 3. Functional outcome. Kaplan-Meier curves for time to Karnofsky Performance Scale (KPS) < 60 by chemotherapy (A), and by extent of radiation (B). Chemotherapy is associated with better KPS outcomes. CSI, craniospinal irradiation; CTx, chemotherapy; IFRT, involved-field RT; RT, radiotherapy; WBRT, whole brain RT; WVRT, whole ventricle RT.

etoposide, and cyclophosphamide. Although therapy-related AML has been associated with exposure to alkylating agents and ionizing radiation, distinguishing therapy-related AML from de novo AML remains challenging in clinical practice.[35,36] Therefore, the causal relationship between prior treatment and the development of AML in this patient cannot be definitively established, and the potential contribution of both chemotherapy and radiation exposure should be interpreted with caution when considering long-term treatment risks.

Prognostic Factors in Patients With iGE

In our cohort, multivariate analysis revealed key prognostic factors affecting outcomes in patients with iGE. Bifocal

tumor location showed a tendency toward poorer OS. For recurrence, suprasellar tumors were associated with a lower CIR compared with other locations, whereas pineal tumors were associated with a higher CISM. However, these findings should be interpreted with caution, as they do not fully consistent with previous literature, which generally reports comparable outcomes between suprasellar and pineal germinomas,[37–39] and may reflect residual confounding inherent to this retrospective study. In particular, the lower CIR in suprasellar tumors and the higher CISM in pineal tumors were not expected based on prior reports, and their underlying mechanisms remain unclear. These discrepancies may be related to differences in treatment patterns, unmeasured confounders, or the limited number of events. Moreover, some covariates showed extremely large or small SHR estimates in the competing risk analysis, particularly for tumor location, surgical intervention, and RT in CIR, as well as for BG-thalamus location, IFRT, and metastatic status in CISM. This likely reflects sparse data and potential model instability, given the relatively small number of events compared with the number of covariates. Accordingly, the magnitude of these associations should be interpreted cautiously, as effect sizes may be over- or under-estimated. Overall, these location-related findings should be considered hypothesis-generating rather than definitive and require validation in larger, independent cohorts.

On the other hand, chemotherapy was independently associated with improved OS and better functional status, likely reflecting both its direct antitumor effect and its role in enabling RT de-intensification. Conversely, compared with patients who received CSI, those received reduced-extent approaches such as WVRT or IFRT had higher recurrence hazard ratios. These findings align with those of multicenter Asian studies that identified RT field size as the key risk factor for relapse in patients with iGE.[19] The functional outcome was favorably impacted by chemotherapy, supporting the notion that systemic treatment enabling lower radiation extent/dose contributes not only to survival but also to long-term quality of life. Metastatic status was not identified as a major prognostic factor, which runs counter to prior study.[19]

In earlier research, a substantial proportion of patients with metastasis died from causes unassociated with tumor progression, raising the question of whether metastatic status truly influences patient prognosis. In addition, during endoscopic third ventriculostomy, we often encountered small, multiple tumor seedings along the ventricular walls that are not visible on MR images. Seeding of iGE may be more common than expected on cerebrospinal fluid analysis or MRI findings and seems curable with treatment. Moreover, although the proportion of metastatic patients in our cohort was comparable to that in previous studies, our institutional policy led to a high rate of chemotherapy usage (76.4% overall, 74.6% for M0, and 85.7% for M+ in our cohort) which may explain why metastatic status did not show a significant difference in prognosis. These findings underscore the importance of tumor location, chemotherapy use, and radiation extent/dose in stratifying treatment for iGE—balancing maximized tumor control with minimal long-term toxicity.

We also explored whether the period of diagnosis influenced survival outcomes. Although a difference in survival was observed between the early (1983-1998) and late (1999-2013) periods in univariate analysis, the diagnosis period was not independently associated with OS after adjusting for clinical variables, RT extent and dose, and the use of chemotherapy (Supplementary Figure S7). This finding suggests that the apparent temporal survival difference may largely reflect evolving treatment strategies rather than the calendar period itself.

Limitations

Several limitations should be acknowledged. Owing to its retrospective design and limited-center setting, our study may be subject to selection bias and may not be fully generalizable to other populations. Furthermore, the KPS score was not consistently documented for all patients and was retrospectively estimated from available clinical information when not explicitly recorded, which may have introduced potential bias. In addition, death was included as part of the composite definition of poor functional outcome, as it may represent the most severe form of functional deterioration, particularly in the context of long-term complications. However, this approach may also introduce survival-driven effects; accordingly, results from analyses excluding deaths should be interpreted alongside the primary findings. To analyze long-term outcomes while avoiding substantial imbalance in patient numbers between the chemotherapy (–) and (+) groups, historical data up to 2013 were included. Chemotherapy has been used routinely at our institutions since 2000. Because this study examined outcomes over an extended period, chemotherapy regimens, radiation extent, and doses evolved during the study period. Additionally, although long-term follow-up data provides meaningful insight into our cohort, they may introduce survivorship bias. Long-term routine follow-up beyond 5 years was not consistently maintained to all patients. As a result, only patients with significant medical problems may have visited the hospital, whereas relatively healthy patients may not have. This may have contributed to the apparent decline in OS and increase in CISM observed during the later phase of follow-up. Nine deaths occurred with undetermined causes, representing another limitation of this study. Despite these limitations, our findings provide important insights into the long-term outcomes, treatment strategies, and survivorship issues in patients with iGE. Future research should address these limitations by conducting multicenter studies with larger sample sizes to further validate and expand our understanding of iGE management and its long-term consequences.

Conclusion

iGE is generally associated with a favorable prognosis. However, serious long-term complications, including endocrine dysfunction, secondary malignancy, psychiatric disorders, and radiation-induced vasculopathy, may arise during long-term follow-up. Extended surveillance and comprehensive survivor care are therefore essential. In particular, patients treated historically with wide-extent, high-dose RT require careful monitoring well beyond 10 years post-treatment. Moreover, providing psychological support

is vital for addressing the emotional and mental health needs of survivors. Treatment strategies incorporating chemotherapy may enable reductions in the extent and dose of radiation while effective tumor control. Such approaches may help mitigate long-term toxicity and improve both survival and quality of life in patients with iGE.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology Advances* (https://academic.oup.com/noa).

Keywords

intracranial germinoma | long-term adverse effects | outcome | secondary malignancy

Author Contributions

Study concept and design: K.-C.W.; I.H.K.; S.-K.K.. Data collection: K.H.K.; K.T.H.; C.-Y.K.; C.-K.P.; J.Y.L.; J.H.P.; B.-K.C.; K.-C.W.; I.H.K.; S.-K.K. Analysis and interpretation of data: Y.S.; K.H.K. Drafting of the manuscript: Y.S., K.H.K., K.-C.W., I.H.K., and S.-K.K. Revising of the manuscript: All authors.

Conflict of Interest Statement

None declared.

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Data Availability

Restrictions apply to the availability of some or all the data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will request details about the restrictions and any conditions under which access to some data may be provided.

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References

1. Dho YS, Jung KW, Ha J, et al. An updated nationwide epidemiology of primary brain tumors in Republic Of Korea, 2013. *Brain Tumor Res Treat*. 2017;5:16-23. https://doi.org/10.14791/btrt.2017.5.1.16
2. Echevarria ME, Fangusaro J, Goldman S. Pediatric central nervous system germ cell tumors: a review. *Oncologist*. 2008;13:690-699. https://doi.org/10.1634/theoncologist.2008-0037
3. Poynter JN, Fonstad R, Tolar J, Spector LG, Ross JA. Incidence of intracranial germ cell tumors by race in the United States, 1992-2010. *J Neurooncol*. 2014;120:381-388. https://doi.org/10.1007/s11060-014-1562-7
4. Cho KT, Wang KC, Kim SK, Shin SH, Chi JG, Cho BK. Pediatric brain tumors: statistics of SNUH, Korea (1959-2000). *Childs Nerv Syst*. 2002;18:30-37. https://doi.org/10.1007/s00381-001-0547-y
5. Zhou Z, Liu J, Yue Q, et al. Optimal treatment approach for intracranial germinoma: a systematic review and meta-analysis. *BMC Cancer*. 2025;25:26. https://doi.org/10.1186/s12885-024-13323-1
6. Pettorini BL, Park YS, Caldarelli M, Massimi L, Tamburrini G, Di Rocco C. Radiation-induced brain tumours after central nervous system irradiation in childhood: a review. *Childs Nerv Syst*. 2008;24:793-805. https://doi.org/10.1007/s00381-008-0631-7
7. You SH, Lyu CJ, Kim DS, Suh CO. Second primary brain tumors following cranial irradiation for pediatric solid brain tumors. *Childs Nerv Syst*. 2013;29:1865-1870. https://doi.org/10.1007/s00381-013-2098-4
8. Sutton LN, Radcliffe J, Goldwein JW, et al. Quality of life of adult survivors of germinomas treated with craniospinal irradiation. *Neurosurgery*. 1999;45:1292-1297. https://doi.org/10.1097/00006123-199912000-00002discussion 1297–1298.
9. Peterson KM, Shao C, McCarter R, MacDonald TJ, Byrne J. An analysis of SEER data of increasing risk of secondary malignant neoplasms among long-term survivors of childhood brain tumors. *Pediatr Blood Cancer*. 2006;47:83-88. https://doi.org/10.1002/pbc.20690
10. Relling MV, Rubnitz JE, Rivera GK, et al. High incidence of secondary brain tumours after radiotherapy and antimetabolites. *Lancet*. 1999;354:34-39. https://doi.org/10.1016/S0140-6736(98)11079-6

11. 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;37:3283-3290. https://doi.org/10.1200/JCO.19.00701
12. Travis LB. The epidemiology of second primary cancers. *Cancer Epidemiol Biomarkers Prev*. 2006;15:2020-2026. https://doi.org/10.1158/1055-9965.EPI-06-0414
13. Sugiyama K, Uozumi T, Arita K, et al. Clinical evaluation of 33 patients with histologically verified germinoma. *Surg Neurol*. 1994;42:200-210. https://doi.org/10.1016/0090-3019(94)90263-1
14. Silber JH, Radcliffe J, Peckham V, et al. Whole-brain irradiation and decline in intelligence: the influence of dose and age on IQ score. *J Clin Oncol*. 1992;10:1390-1396. https://doi.org/10.1200/JCO.1992.10.9.1390
15. Kun LE, Mulhern RK, Crisco JJ. Quality of life in children treated for brain tumors. Intellectual, emotional, and academic function. *J Neurosurg*. 1983;58:1-6. https://doi.org/10.3171/jns.1983.58.1.0001
16. Malbari F, Gershon TR, Garvin JH, et al. Psychiatric manifestations as initial presentation for pediatric CNS germ cell tumors, a case series. *Childs Nerv Syst*. 2016;32:1359-1362. https://doi.org/10.1007/s00381-016-3145-8
17. Shimizu H, Motomura K, Ohka F, et al. Long-term survival in patients with primary intracranial germ cell tumors treated with surgery, platinum-based chemotherapy, and radiotherapy: a single-institution study. *J Neurosurg*. 2021;135:449-457. https://doi.org/10.3171/2020.6.JNS20638
18. Yamaguchi S, Okamoto M, Ishi Y, et al. Long-term consequences of residual lesions after chemoradiotherapy in patients with germinoma at onset. *J Neurosurg Pediatr*. 2022;30:517-524. https://doi.org/10.3171/2022.8.PEDS22301
19. Koh KN, Wong RX, Lee DE, et al. Outcomes of intracranial germinoma-A retrospective multinational Asian study on effect of clinical presentation and differential treatment strategies. *Neuro Oncol*. 2022;24:1389-1399. https://doi.org/10.1093/neuonc/noab295
20. Bitterman DS, Chi SN, Haas-Kogan DA. A central role of radiation therapy in central nervous system germinoma. *Int J Radiat Oncol Biol Phys*. 2019;104:970-971. https://doi.org/10.1016/j.ijrobp.2019.05.020
21. Wolden SL, Wara WM, Larson DA, Prados MD, Edwards MS, Sneed PK. Radiation therapy for primary intracranial germ-cell tumors. *Int J Radiat Oncol Biol Phys*. 1995;32:943-949. https://doi.org/10.1016/0360-3016(95)00067-9
22. Calaminus G, Kortmann R, Worch J, et al. SIOP CNS GCT 96: final report of outcome of a prospective, multinational nonrandomized trial for children and adults with intracranial germinoma, comparing craniospinal irradiation alone with chemotherapy followed by focal primary site irradiation for patients with localized disease. *Neuro Oncol*. 2013;15:788-796. https://doi.org/10.1093/neuonc/not019
23. Acharya S, DeWees T, Shinohara ET, Perkins SM. Long-term outcomes and late effects for childhood and young adulthood intracranial germinomas. *Neuro Oncol*. 2015;17:741-746. https://doi.org/10.1093/neuonc/nou311
24. Kawabata Y, Takahashi JA, Arakawa Y, Shirahata M, Hashimoto N. Long term outcomes in patients with intracranial germinomas: a single institution experience of irradiation with or without chemotherapy. *J Neurooncol*. 2008;88:161-167. https://doi.org/10.1007/s11060-008-9542-4
25. Cheng S, Kilday JP, Laperriere N, et al. Outcomes of children with central nervous system germinoma treated with multi-agent chemotherapy followed by reduced radiation. *J Neurooncol*. 2016;127:173-180. https://doi.org/10.1007/s11060-015-2029-1
26. Frappaz D, Dhall G, Murray MJ, et al. EANO, SNO and Euracan consensus review on the current management and future development of intracranial germ cell tumors in adolescents and young adults. *Neuro Oncol*. 2022;24:516-527. https://doi.org/10.1093/neuonc/noab252
27. Eom KY, Kim IH, Park CI, et al. Upfront chemotherapy and involved-field radiotherapy results in more relapses than extended radiotherapy for intracranial germinomas: modification in radiotherapy volume might be needed. *Int J Radiat Oncol Biol Phys*. 2008;71:667-671. https://doi.org/10.1016/j.ijrobp.2008.01.061
28. Minniti G, Traish D, Ashley S, Gonsalves A, Brada M. Risk of second brain tumor after conservative surgery and radiotherapy for pituitary adenoma: update after an additional 10 years. *J Clin Endocrinol Metab*. 2005;90:800-804. https://doi.org/10.1210/jc.2004-1152
29. Matsutani M. Japanese pediatric brain tumor study G. Combined chemotherapy and radiation therapy for CNS germ cell tumors—the Japanese experience. *J Neurooncol*. 2001;54:311-316.
30. Lee JH, Eom KY, Phi JH, et al. Long-term outcomes and sequelae analysis of intracranial germinoma: need to reduce the extended-field radiotherapy volume and dose to minimize late sequelae. *Cancer Res Treat*. 2021;53:983-990. https://doi.org/10.4143/crt.2020.1052
31. Diez B, Balmaceda C, Matsutani M, Weiner HL. Germ cell tumors of the CNS in children: recent advances in therapy. *Childs Nerv Syst*. 1999;15:578-585. https://doi.org/10.1007/s003810050546
32. Fouladi M, Grant R, Baruchel S, et al. Comparison of survival outcomes in patients with intracranial germinomas treated with radiation alone versus reduced-dose radiation and chemotherapy. *Childs Nerv Syst*. 1998;14:596-601. https://doi.org/10.1007/s003810050279
33. Jinguji S, Yoshimura J, Nishiyama K, et al. Factors affecting functional outcomes in long-term survivors of intracranial germinomas: a 20-year experience in a single institution. *J Neurosurg Pediatr*. 2013;11:454-463. https://doi.org/10.3171/2012.12.PEDS12336
34. Lee DS, Lim DH, Kim IH, et al. Upfront chemotherapy followed by response adaptive radiotherapy for intracranial germinoma: prospective multicenter cohort study. *Radiother Oncol*. 2019;138:180-186. https://doi.org/10.1016/j.radonc.2019.06.002
35. Badie C, Gale RP. What is radiation-induced acute myeloid leukaemia/can it be accurately identified? *Leukemia*. 2025;39:1334-1336. https://doi.org/10.1038/s41375-025-02561-2
36. Jerez J, Hernandez C, Hill CN. Understanding therapy-related AML: genetic insights and emerging strategies for high-risk patients. *Front Hematol*. 2025;4:1609642. https://doi.org/10.3389/frhem.2025.1609642
37. Che W, Wang Y, Zhou Y, Wang X, Lyu J. 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*. 2022;29:10732748221095944. https://doi.org/10.1177/10732748221095944
38. Lee SH, Jung K-W, Ha J, et al. Nationwide population-based incidence and survival rates of malignant central nervous system germ cell tumors in Korea, 2005-2012. *Cancer Res Treat*. 2017;49:494-501. https://doi.org/10.4143/crt.2016.129
39. Ono N, Kakegawa T, Zama A, et al. Factors affecting functional prognosis in survivors of primary central nervous system germinal tumors. *Surg Neurol*. 1994;41:9-15. https://doi.org/10.1016/0090-3019(94)90201-1

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