

# Emergency irradiation with 3.4 Gy/2f in sellar/suprasellar germinoma patients with rapid visual acuity decline

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## Abstract

**Background:** Rapid visual acuity (VA) decline was a common complaint in patients with sellar/suprasellar germinoma. In our hospital, 3.4 Gy/2f of emergency irradiation was applied to save patient VA and enable subsequent chemoradiotherapy. This study aimed to investigate the efficacy of emergency irradiation with 3.4 Gy/2f in patients with sellar/suprasellar germinoma who had rapid VA decline.

**Methods:** From January 2014 to December 2017, 33 patients with sellar/suprasellar germinoma who complained of VA decline within 3 months received 3.4 Gy/2f of emergency irradiation in Beijing Tiantan Hospital. The best-corrected VA (BCVA) and mean deviation (MD) were measured. Correlations between visual function change and clinical factors, including age at diagnosis, duration of VA decline, extent of tumor regression, serum level of tumor markers, were analyzed.

**Results:** Among 33 patients with sellar/suprasellar germinoma, the median diameter and volume of sellar/suprasellar lesions were 32 mm (range: 5–55 mm) and 12.9 cm<sup>3</sup> (range 0.6–58.5 cm<sup>3</sup>), respectively. Data on pre- and post-emergency-irradiation BCVA were obtained in 32 patients. For the right eyes, BCVA was improved in 23 patients (71.9%), unchanged in 7 (21.9%), and worsened in 2 (6.2%); and for the left eyes, these numbers were 27 (84.4%), 4 (12.5%), and 1 (3.1%), respectively. In terms of the logarithm of the minimum angle of resolution (logarithm of the minimum angle of resolution = Log (1/BCVA) score, the improvement was significant in both eyes ( $P < 0.001$ ). In terms of MD, six patients had paired data and the improvement was marginal in the right eyes ( $P = 0.068$ ) and significant in the left eyes ( $P = 0.043$ ). However, no clinical factor was found to have correlation with visual function improvement.

**Conclusion:** In sellar/suprasellar germinoma patients with VA decline, 3.4 Gy/2f of emergency irradiation was effective in improving visual function.

**Keywords:** Germinoma; Sellar/suprasellar; Radiotherapy; Chemotherapy; Visual acuity; Beta-human chorionic gonadotropin

## Introduction

Primary intra-cranial germ cell tumors (GCTs) are rare malignancies that are mostly identified in children and adolescents. According to the 2016 World Health Organization (WHO) classification for tumors of the central nervous system, GCTs are histologically classified into germinoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, teratoma, teratoma with malignant transformation, and mixed GCT.<sup>[1]</sup> In brief, GCTs can also be divided into two broad groups: germinoma and non-germinatous germ cell tumors (NGGCTs). Germinoma is the most common sub-type of GCTs and accounts for two-thirds of all cases.<sup>[2]</sup> Due to the higher sensitivity of tumor cells to chemoradiotherapy, patients with germinoma have excellent prognoses, and the 5-year overall survival rate is greater than 90%.<sup>[3]</sup>

The sellar/suprasellar region is one of the most commonly involved areas of germinoma.<sup>[4,5]</sup> Visual function impairments such as visual acuity (VA) decline and visual field defects were common complaints from patients with sellar/suprasellar germinoma.<sup>[6,7]</sup> Furthermore, certain patients experienced rapid VA deterioration due to rapid progression of tumor cells. In clinical practice, this situation must be addressed immediately to avoid irreversible loss of visual function. Although surgery is an option that can debulk the tumor and obtain histological diagnosis, selected studies found that patients might experience a rapid deterioration in vision after tumor depression.<sup>[8]</sup> Furthermore, tumor re-growth during the post-operation recovery period was another concern and might compromise the role of surgery. Chemotherapy is an alternative measure because germinoma is highly sensitive to anti-

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tumor agents. However, in patients with sellar/suprasellar germinoma, poorer general conditions at diagnosis are usually present, which are believed to be secondary to adipsic diabetes insipidus and endocrinopathy. Hence, significant risk is associated with the administration of systemic therapy such as chemotherapy. Thus, in our center, emergency irradiation of 3.4 Gy/2f was applied initially and was intended to preserve visual function and also enable subsequent anti-tumor therapy. This study presented the results from 33 patients who were diagnosed and treated in our hospital and were studied retrospectively.

## Methods

### Ethical approval

This study was reviewed and approved by the Institutional Review Board of Beijing Tiantan Hospital (Grant number: KY 2018-064-02). The patient informed written consent was waived by the Institutional Review Board of Beijing Tiantan Hospital.

### Study population

Medical records from patients who were diagnosed with germinoma at Beijing Tiantan Hospital between January 2014 and December 2017 were screened. The inclusion criteria were as follows: (1) age <30 years, (2) primary lesion located in the sellar/suprasellar region, (3) elevation of serum beta-human chorionic gonadotropin ( $\beta$ -HCG; normal value <5.0 U/L) or placental alkaline phosphatase (PLAP; normal value 30.0–114.0 U/L), (4) mandatory pathology for patients with negative serum tumor markers, (5) severe and acute VA decline within 3 months, and (6) emergency irradiation administered due to vision acuity decline. The exclusion criteria were as follows: (1) primary lesion located in an area other than the sellar/suprasellar region, (2) mild and chronic VA decline, (3) elevated alpha-fetoprotein (AFP), or (4) chemotherapy as the initial treatment modality. Due to the rapid visual function deterioration that characterized patients in our cohort, the diagnosis of germinoma was established mostly based on clinical presentations such as signs and symptoms, tumor site, tumor markers, and radiological findings. Clinical data from eligible patients were obtained from the institutional archive and analyzed retrospectively.

### Treatment strategy

Before treatment, all patients underwent a baseline evaluation, including medical history, general physical examination, VA examination, complete blood count, serum chemistry, serum tumor markers ( $\beta$ -HCG, AFP, and PLAP), endocrine function evaluation (thyrotrope, corticotrope, somatotrope, gonadotrope, and lactotrope), and radiographic examinations (plain computed tomography scan, enhanced-contrast magnetic resonance imaging [MRI]). Humphrey perimetry was optional. Emergency irradiation of 3.4 Gy/2f was subsequently administered to the primary lesions. Approximately 1 week later, the baseline evaluations were repeated, and spinal MRI was performed. For patients with tumor regression, two cycles

of platinum-based chemotherapy were administered followed by radiotherapy. Otherwise, surgery was considered. Radiotherapy consisted of whole-brain irradiation with a dose of 24 to 30 Gy and a boost to the primary lesions. The total prescription dose reached 40 Gy for patients who had complete remission (CR) to chemotherapy and 50 Gy for those with less than CR. Patients with disseminated disease also received cranial spinal irradiation (CSI) to the entire cranial contents and spinal axis. After completion of radiotherapy, up to four cycles of platinum-based chemotherapy was recommended. A routine follow-up was repeated every 3 months for the first 2 years and every 6 months for the next 3 years.

### Visual examination

The standard VA chart was used to collect best-corrected VA (BCVA). For statistical analysis, the logarithm of the minimum angle of resolution (LogMAR) was used and was converted from BCVA according to the formula  $\text{LogMAR} = \text{Log}(1/\text{BCVA})$ . The counter finger at 2 feet was equal to 2.0 of LogMAR. Hand motion at 2 feet was equal to 3.0 of LogMAR. Light perception and no light perception were excluded for statistical analysis because they are not actually VA measurements. Humphrey perimetry was used in visual field examination. The mean deviation (MD) was applied for assessment of the visual field defect.

### Statistical analysis

IBM SPSS Statistics version 19.0 software (IBM Corp., Armonk, NY, USA) was used for the data analysis. The non-normal distribution data were shown as median (range), and the normal distribution data were shown as mean  $\pm$  standard deviation. The Wilcoxon rank sum test was used to compare continuous variables, and the Chi-square test was used to compare categorical variables. The Spearman rank correlation test was applied to analyse the correlation between visual function change and clinical factors such as age at diagnosis (years), duration of VA decline (from the date of awareness of VA decline to the date of diagnosis) (months), extent of tumor regression, and serum levels of tumor markers ( $\beta$ -HCG and PLAP). The response assessment in neuro-oncology criteria was used in the response evaluation. A  $P < 0.05$  was considered as statistical significance, and all statistical tests were two-sided.

## Results

### Patient characteristics

The study included 33 patients with a median follow-up period of 19 months (range: 3–42 months). The median age of this group was 11 years (range: 5–27 years) with a majority of female patients (24/33, 72.7%). The median diameter and volume of sellar/suprasellar lesions were 32 mm (range: 5–55 mm) and 12.9 cm<sup>3</sup> (range: 0.6–58.5 cm<sup>3</sup>), respectively. Overall, tumor markers were elevated in 93.9% (31/33) of patients. The median levels of  $\beta$ -HCG and PLAP were 14.2 U/L (range: 5.5–222.0 U/L) and 137.0 U/L (range: 120.0–326.0 U/L), respectively.

Both patients with negative tumor markers were diagnosed with germinoma after initial surgery and had progressive disease 4 and 5 months later, respectively (did not comply with the suggestion of post-surgery chemoradiotherapy).

In addition to VA decline, adipsic diabetes insipidus was another symptom reported by all patients with a median duration of 10 months (range: 1–48 months) before diagnosis. As a result, up to 60.6% (20/33) of patients also had hypernatremia. Endocrine examination found that 66.7% (22/33) patients had T3/T4 deficiency and 81.8% (27/33) had cortisol deficiency, respectively. Furthermore, ten patients had psychological symptoms such as drowsy (7/10), agitation (1/10), fatigue (1/10), and dizzy (1/10). One patient had cachexia, which was believed to be secondary to pituitary abnormalities.

### Treatment results

At a median of 7 days (range: 3–25 days) after emergency irradiation, the median percentage of tumor remission was 55.0% (range: 15.0%–90.0%), of which partial remission (PR) was achieved in 72.7% (24/33) patients with stable disease achieved in the remainder. Subsequently, 26 patients received two cycles of chemotherapy, and three received one cycle. Before chemoradiotherapy, CR was achieved in 23 patients, and six patients still had residual disease (<0.5 cm). Four patients received no chemotherapy prior to radiotherapy because of creatinine elevation ( $n = 2$ ), leukopenia ( $n = 1$ ), or tachycardia ( $n = 1$ ). In terms of radiotherapy, 22 patients received a total dose of 40 Gy, eight received 50 Gy, and three received CSI. No patients relapsed or died [Figure 1 shows a typical case].

### Vision acuity

Data on pre- and post-emergency-irradiation BCVA were obtained in 32 patients, except for one 5-year girl who failed to cooperate with the examination. In terms of the right eye, BCVA was improved in 23 patients (71.9%), unchanged in 7 (21.9%) and worsened in 2 (6.2%); and for the left eye, these numbers were 27 (84.4%), 4 (12.5%), and 1 (3.1%), respectively. If improvement was defined as achieved in at least one eye, 30 patients (93.8%) achieved improvement. One patient (3.1%) was unchanged in both

eyes. The other patient (3.1%) had one eye unchanged and one eye worsened [Table 1].

For the LogMAR score, the median pre- and post-emergency-irradiation LogMAR scores of the right eyes were 0.8 (range: –0.1 to 3.0) and 0.3 (range: –0.1 to 3.0), respectively, and these numbers in the left eyes were 0.7 (range: 0 to 3.0) and 0.3 (range: 0 to 3.0), respectively. The LogMAR score improvement reached a significant level in both eyes ( $P < 0.001$ ) [Table 1].

To further explore the factors that might show a correlation with LogMAR score improvement, Spearman rank correlation test was conducted to compare LogMAR score improvement with the age at diagnosis, duration of VA decline, extent of tumor regression, and serum level of tumor markers ( $\beta$ -HCG and PLAP). Unfortunately, none of these factors was found to show correlation with LogMAR score improvement [Table 2].

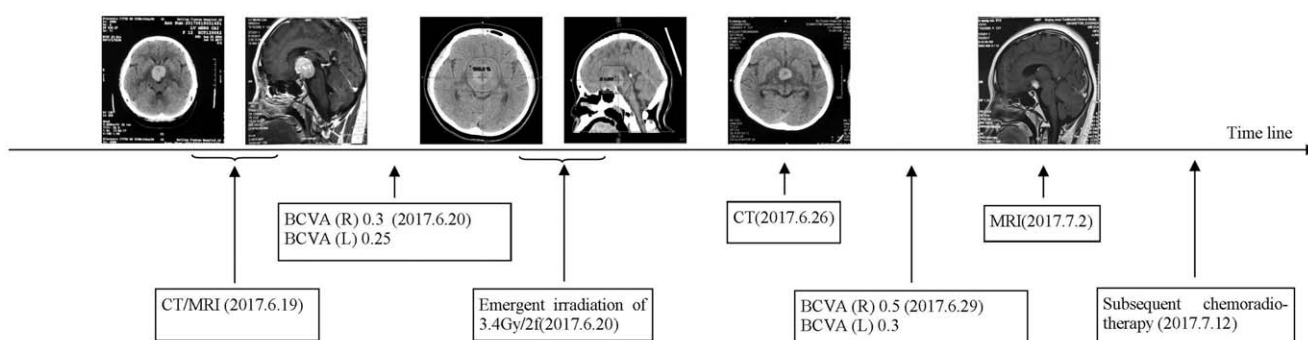
### Visual field defects

Post-emergency-irradiation Humphrey perimetry data were available in 19 patients, whereas pre-emergency-irradiation data were available in only six patients. In six patients with paired data, MD improvement was marginal in the right eyes ( $n = 5$ , one patient had no light perception in the right eye;  $P = 0.068$ ) and reached a significant level in the left eyes ( $P = 0.043$ ) [Table 1]. However, no clinical factor showed correlation with MD change (data not shown).

### Discussion

In our study, we investigated the efficacy of emergency irradiation with 3.4 Gy/2f in patients with sellar/suprasellar germinoma who had rapid visual function deterioration. The results showed that this modality was effective in saving patient visual function because VA and visual field defects were improved significantly.

In addition to pineal or basal ganglia regions, the sellar/suprasellar region is one of the most commonly involved sites in patients with germinoma, especially for female



**Figure 1:** Typical case: a 12-year girl complained of diabetes insipidus for approximately 1 year and presented with fever (39°C), drowsy, memory impairment, and visual acuity decline 1 month before admission. Radiographic examination found sellar/suprasellar lesions, and serum  $\beta$ -HCG was 11.3 U/L. After emergency irradiation, the sellar/suprasellar lesions shrunk, and BCVA improved from 0.30 to 0.50 on the right and from 0.25 to 0.30 on the left. BCVA: Best-corrected visual acuity;  $\beta$ -HCG: Beta-human chorionic gonadotropin.

**Table 1: Comparison of visual function before and after emergency irradiation.**

Parameters	Pre-emergency-irradiation	Post-emergency-irradiation	Statistical values	P
BCVA (right eyes) (n = 32), n (%)			14.266*	0.047
≥1.00	4 (12.5)	7 (21.9)		
0.80–0.99	2 (6.2)	5 (15.7)		
0.60–0.79	1 (3.1)	1 (3.1)		
0.30–0.59	5 (15.7)	6 (18.8)		
<0.30	17 (53.2)	11 (34.3)		
Hand motion	1 (3.1)	1 (3.1)		
Count fingers	1 (3.1)	0		
Light perception	0	0		
No light perception	1 (3.1)	1 (3.1)		
BCVA (left eyes) (n = 32), n (%)			22.733*	0.002
≥1.00	1 (3.1)	5 (15.7)		
0.80–0.99	2 (6.2)	5 (15.7)		
0.60–0.79	1 (3.1)	2 (6.2)		
0.30–0.59	5 (15.7)	6 (18.8)		
<0.30	16 (50.0)	10 (31.2)		
Hand motion	2 (6.2)	1 (3.1)		
Count fingers	1 (3.1)	1 (3.1)		
Light perception	0	0		
No light perception	4 (12.6)	2 (6.2)		
LogMAR score, median (range)				
Right eye (n = 31)	0.8 (-0.1, 3.0)	0.3 (-0.1, 3.0)	-4.199†	<0.001
Left eye (n = 28)	0.7 (0, 3.0)	0.3 (0, 3.0)	-3.800†	<0.001
MD, median (range)				
Right eyes (n = 5)	-21.6 (-22.6, -7.0)	-10.6 (-16.3, -1.8)	-1.826†	0.068
Left eyes (n = 6)	-16.0 (-29.5, -11.2)	-12.7 (-17.2, -0.9)	-2.023†	0.043

\*  $\chi^2$  values. † Z values. BCVA: Best-corrected visual acuity; LogMAR: Logarithm of the minimum angle of resolution; MD: Mean deviation.

**Table 2: Correlation between LogMAR improvement and clinical factors.**

Parameters	LogMAR improvement (right eyes, n = 31)		LogMAR improvement (left eyes, n = 28)	
	Correlation coefficient	P	Correlation coefficient	P
Age at diagnosis	-0.006	0.970	0.252	0.190
Duration of visual acuity decline	0.244	0.310	-0.301	0.250
Extent of tumor regression	-0.231	0.210	-0.155	0.430
Serum level of $\beta$ -HCG	-0.259	0.210	-0.384	0.078
Serum level of PLAP	-0.243	0.240	-0.024	0.910

LogMAR: Logarithm of the minimum angle of resolution;  $\beta$ -HCG: Beta-human chorionic gonadotropin; PLAP: Placental alkaline phosphatase.

patients.<sup>[5,9]</sup> Due to impairment of anti-diuretic hormone secretion, more than 80% of patients concomitantly presented with central diabetes insipidus and loss of thirst sensation.<sup>[10]</sup> However, these signs were always missed by parents, guardians, or even inexperienced doctors. As a result, this condition received minimal attention until visual function decreased dramatically due to rapid progression of the intra-cranial tumor mass in certain patients. In a study conducted by Frappaz *et al*,<sup>[6]</sup> among seven patients who suffered vision loss, five had suprasellar lesions. In another study including 16 patients with sellar/suprasellar germinoma, eight had visual complaints.<sup>[7]</sup> Furthermore, at the time of visual function deterioration, symptoms associated with impairment of anti-diuretic hormone secretion and anterior pituitary insufficiency were also aggravated, which resulted in poorer general

condition. Thus, it is believed that a higher risk must be accepted for the subsequent anti-tumor therapy, especially systemic therapy.

Few studies have investigated the optimal treatment strategy in sellar/suprasellar germinoma patients with visual function impairment. Considering the higher sensitivity of germinoma to radiation, an emergency irradiation strategy was applied in our center. In two consecutive days, a total of 3.4 Gy was delivered to the primary lesion. At the time of re-evaluation approximately 1 week later, more than 90% of patients showed improved or stable VA. According to the WHO classification, BCVA lower than 0.3 is classified as low vision or blindness. As shown in our study, the proportion of BCVA less than 0.3 decreased from near 70% to approximately 40%. The

Chi-square test found that the proportion of eyes with better classification improved significantly on both sides. Furthermore, the improvement in LogMAR score reached a significant level in both eyes. In terms of visual field defect, the MD improvement was also statistically significant, although data were available in only six patients.

In patients with sellar/suprasellar lesions, the diagnosis of germinoma is still a challenge for oncologists, especially for patients with negative tumor markers. Lee *et al*<sup>[11]</sup> found that only 30% of patients had tumor marker elevation. In our hospital, the number of patients with sellar/suprasellar lesion and visual function impairment without tumor marker elevation was at least twice that enrolled in this study at the same period. Although biopsy is an option, high risk must be accepted due to critical brain and cranial nerve structures adjacent to the pituitary area. Moreover, in patients with visual function impairment, the loss might be irreversible during pathology diagnosis. Diagnostic radiotherapy is another alternative measure that was first reported by Japanese authors in the 1990s.<sup>[12]</sup> After delivery of a dose of 20 Gy/10f, the diagnosis of germinoma or mixed GCTs with germinoma component was considered if tumor regression was observed. Otherwise, NGGCTs or tumors other than GCTs were considered, and surgical intervention should be weighed. However, for diagnostic purposes such as this, the dosage is too high, and the potential side effects are a concern. Furthermore, a dilemma might emerge if the diagnosis was adjusted and re-irradiation is necessary for the following treatment. In addition, the 20 Gy/10f regimen lasts two weeks, which might cause a delay in intervention from other procedures if patients had minor responses or no responses. Thus, we attempted to lower the dose from 10 Gy/5f to 3.4 Gy/2f in 18 years.<sup>[13,14]</sup> We found that 10 Gy/5f had efficacy comparable to 20 Gy/10f in terms of tumor regression in which over 90% of lesions shrunk by more than 50%. As shown in our study, 72.7% of patients achieved PR when 3.4 Gy/2f was delivered. Although the response rate was lower than that of 20 Gy/10f, 3.4 Gy/2f might be more reasonable for “diagnostic radiotherapy” because the main purpose was diagnosis other than efficacy. Otherwise, this approach had minimum effect on subsequent medical procedures if the diagnosis was adjusted.

In terms of treatment, CSI used to be the standard care for patients with germinoma, with a cure rate of over 90%.<sup>[15,16]</sup> However, the toxicities of CSI are a concern. Many authors have found that the addition of chemotherapy could make dose and/or field reduction possible without compromising long-term survival in patients with localized lesions.<sup>[3,17,18]</sup> In our cohort, the treatment modality includes induction chemotherapy, radiotherapy, and maintenance chemotherapy. In addition to reducing the dose and/or field of radiotherapy, the potential role of induction chemotherapy might include extinguishing possible micro-metastasis and testing tumor sensitivity to anti-tumor therapy. In patients with residual disease after induction chemotherapy, the histological content other than germinoma can be considered, and the dose of radiotherapy can be escalated. However, Saeki *et al*<sup>[7]</sup>

found that patients with sellar/suprasellar lesions larger than 20 mm had poorer performance status. In our study, the median maximum diameter of the sellar/suprasellar lesions was 32 mm (range: 5–55 mm). Although the performance status was not evaluated, a higher proportion of patients presented symptoms associated with impairment of anti-diuretic hormone secretion and anterior pituitary insufficiency, and certain complications were severe. Under these circumstances, a higher risk is encountered if systemic therapy is administered immediately. In our study, at the time of emergency irradiation delivery, replacement therapy and supportive care were administered concomitantly. At the time of baseline re-evaluation, the general condition was improved, and 29/33 patients received subsequent induction chemotherapy. Therefore, we believed that this approach is an optimal treatment strategy, especially in such an emergency situation.

In conclusion, this study showed that emergency irradiation with 3.4 Gy/2f had satisfactory efficacy in saving patient visual function and paving the way for subsequent anti-tumor therapy.

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### Conflicts of interest

None.

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