

Clinical Investigation: Central Nervous System Tumor

# Salvage Treatment for Recurrent Intracranial Germinoma After Reduced-Volume Radiotherapy: A Single-Institution Experience and Review of the Literature

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## Summary

We retrospectively reviewed 14 patients with recurrent intracranial germinoma after reduced-volume radiotherapy at our institution and an additional 88 patients in the literature. The study showed that a substantial portion of recurrences developed more than 5 years after initial treatment. The treatment response to both radiotherapy and chemotherapy was generally good. Salvage craniospinal irradiation with or without

**Purpose:** Intracranial germinomas (IGs) are highly curable with radiotherapy (RT). However, recurrence still occurs, especially when limited-field RT is applied, and the optimal salvage therapy remains controversial.

**Methods and Materials:** Between January 1989 and December 2010, 14 patients with clinically or pathologically diagnosed recurrent IGs after RT were reviewed at our institution. Of these, 11 received focal-field RT, and the other 3 received whole-brain irradiation, whole-ventricle irradiation, and Gamma Knife radiosurgery as the respective first course of RT. In addition, we identified from the literature 88 patients with recurrent IGs after reduced-volume RT, in whom the details of salvage therapy were recorded.

**Results:** The median time to recurrence was 30.3 months (range, 3.8–134.9 months). One patient did not receive further treatment and was lost during follow-up. Of the patients, 7 underwent salvage with craniospinal irradiation (CSI) plus chemotherapy (CT), 4 with CSI alone, 1 with whole-brain irradiation plus CT, and 1 with Gamma Knife radiosurgery. The median follow-up time was 105.1 months (range, 24.2–180.9 months). Three patients died without evidence of disease progression: two from second malignancies and one from unknown cause. The others remained disease free. The 3-year survival rate after recurrence was 83.3%. A total of 102 patients from our study and the literature review were analyzed to determine the factors affecting prognosis and outcomes. After recurrence, the 5-year survival rates were 71% and 92.9% for all patients and for those receiving salvage CSI, respectively. Univariate analysis showed that initial RT volume, initial RT dose, initial CT, and salvage RT type were significant

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chemotherapy was associated with excellent survival.

prognostic predictors of survival. On multivariable analysis, salvage CSI was the most significant factor ( $p = 0.03$ ).

**Conclusions:** Protracted follow-up is recommended because late recurrence is not uncommon. CSI with or without CT is an effective salvage treatment for recurrence after reduced-volume RT. © 2012 Elsevier Inc.

**Keywords:** Germinoma, Recurrence, Salvage treatment, Radiotherapy, Craniospinal irradiation

## Introduction

Intracranial germinomas (IGs) are sensitive to both radiotherapy (RT) and chemotherapy (CT). A recurrence rate of less than 5% to 10% can be achieved with craniospinal irradiation (CSI), whole-brain irradiation (WBI), or whole-ventricle irradiation (WVI) plus focal boost, with or without CT (1). With an intent to reduce neurocognitive and endocrine dysfunction after extensive-field RT, treatment with primary CT or focal RT alone was once used but led to an unacceptably high recurrence rate of approximately 20% to 50% (1, 2). A combination of CT and focal RT is still insufficient to prevent recurrences, mainly in the ventricles (3–5). Patients with relapse disease usually underwent various salvage treatment, including RT, CT, high-dose chemotherapy (HDC) followed by autologous hematopoietic stem cell rescue, or a combination thereof. Although the salvage rate of IGs is generally higher than that of other central nervous system malignancies, there is a paucity of literature with regard to the details of salvage modalities, complications, and long-term outcomes. Furthermore, the scarcity of recurrent IGs hampers the possibility of determining the optimal salvage strategy.

In this study we first described the characteristics and treatment outcomes of 14 patients with recurrent IGs at our institution. We then performed a literature review and identified 88 additional cases that recurred after initial treatment with reduced-volume RT for further analysis. Our goal was to explore the best management for this patient population. Recurrence after CSI is rare, and the treatment options are very limited because of the cumulative effect of RT. Recurrence after primary CT can be readily salvaged with conventional treatment (2). Thus the two previously mentioned scenarios will not be discussed in this study.

## Methods and Materials

### Patient characteristics

A total of 103 patients with IGs were identified from a review of medical records between January 1989 and December 2010. Of these, 14 had at least one relapse. Except for 1 patient who was referred to our hospital at the time of recurrence, all patients received the whole course of treatment at our institution. There were 12 male and 2 female patients. The median age at initial diagnosis was 14.5 years (range, 5–26 years). All patients received whole-neuraxis magnetic resonance imaging (MRI) to exclude disseminated disease. Nine patients had a pathologically proved IG, whereas the others were diagnosed with clinical assessments and imaging studies. The primary tumor location was the pineal region in 4, suprasellar region in 4, basal ganglia in 2, optic tract in 1, and more than 1 site in 3 cases. The level of serum

$\beta$  human chorionic gonadotropin ( $\beta$ -hCG) was elevated ( $>10$  mIU/mL) in 4 patients, whereas the level of  $\alpha$ -fetoprotein was normal ( $<10$  IU/L) in all. RT was administered as a part of initial treatment in 12 patients, including preceding partial resection in 2, neoadjuvant CT in 1, and adjuvant CT in 2. The other 2 patients received their first course of RT for recurrent disease after primary CT. The volume of RT was focal field in 11 patients, whereas WBI, WVI, and Gamma Knife radiosurgery (GKRS) were used in each of the other 3, respectively. No recurrence was observed in patients treated with CSI. Complete response (CR) after RT was achieved in 13 patients. One patient had a partial response and subsequently received GKRS. The failure patterns and outcomes of salvage treatments were assessed. The characteristics of these 14 patients are summarized in Table 1.

### Literature review

A PubMed search of articles published in English from January 1, 1995, to August 1, 2011, was performed by use of the keywords “germinoma” and “radiotherapy.” A total of 782 articles were identified. To be included in this review, studies had to provide the details of salvage methods and outcomes for patients with recurrent IGs after reduced-volume RT. Cases with recurrence after primary CT or initial CSI were excluded. We also excluded case reports and repeated publications. Manuscripts from the same institution were carefully reviewed to avoid inclusion of the same patient twice. A total of 88 patients were included from 13 studies: 25 from Kamoshima *et al.* (6), 11 from Shikama *et al.* (7) (6 of 17 patients were excluded because of recurrence after initial CSI), 10 from Alapetite *et al.* (5), 9 from Jensen *et al.* (4), 7 from Modak *et al.* (8) (2 of 9 patients were excluded because of recurrence after initial CSI or no recurrence after first course of RT), 5 from Cho *et al.* (9), 4 from Nguyen *et al.* (10), 4 from Nakamura *et al.* (11), 4 from Kawabata *et al.* (12), 3 from Osuka *et al.* (13) (2 of 5 patients were excluded because of primary CT), 2 from Douglas *et al.* (14), 2 from Timmerman *et al.* (15) (1 patient was excluded because of revision of diagnosis to malignant teratoma), and 2 from Fouladi *et al.* (16). Because the study of Ogawa *et al.* (17) focused on spinal recurrence and shared the same database with the study of Shikama *et al.*, it was not included in the analysis.

### Statistical analysis

Survival after recurrence was estimated by use of the Kaplan-Meier method. Difference between survival curves was analyzed with the log-rank test. Variables affecting survival were evaluated with the univariate and multivariate Cox proportional hazards regression model. Statistical analyses were performed with SPSS software (version 17.0; SPSS, Chicago, IL).

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