# Management of Intracranial Germ Cell Tumors at the King Chulalongkorn Memorial Hospital

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***Objective:*** *To study the outcome of less aggressive radiotherapy combined with surgery and chemotherapy to reduce radiation complication in the treatment of intracranial germ cell tumor (ICGCT) at the King Chulalongkorn Memorial Hospital.*
***Material and Method:*** *A descriptive study was established by reviewing patients' records from the Division of Therapeutic Radiology and Oncology admitted between 2001 and 2008. Median follow-up time was 65 months. Patient characteristics, investigations, and treatment modalities were presented in proportion. Survival analysis was evaluated by Kaplan-Meier method. The results were compared with the previous study in done in 1990 to 2000.*
***Results:*** *Forty-two records were reviewed and 71% were male. The median age was 16 years. Pineal region was the most common site in 55%. Interestingly, 12% had synchronous lesions at both pineal and suprasellar regions. Out of 41 patients who had histopathological confirmation, 71% were germinoma. Out of 37 patients who had MRI spine or CSF cytology, 43% had CNS dissemination. Less aggressive radiotherapy combined with surgery and chemotherapy was increasingly utilized; however, five-year overall survival rate in all patients was 83%, comparable to 82% from the previous study. Survival rates of patients without CNS dissemination were 88% in the present study and 83% in the previous study. Survival rates adjusted for histopathology were 86% for germinoma and 76% for non-germinoma.*
*Conclusion: Less aggressive radiotherapy combined with surgery and chemotherapy to reduce radiation complication is an effective treatment for ICGCT.*

***Keywords:*** *Intracranial germ cell tumors, Whole ventricular radiation, Management*

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Intracranial germ cell tumors (ICGCT) are relatively rare. The incidence is approximately 2 to 3% of all intracranial tumors. It also varies among different populations with a higher incidence in Asians[1,2]. ICGCT are mostly found in the second decade of life. They are divided into germinoma and non-germinoma[3]. The latter has a worse prognosis and requires more aggressive treatment. Multimodality treatments are composed of surgery, chemotherapy, and radiotherapy[4]. Radiotherapy has long been an important part of the treatment for germinoma whereas surgery and chemotherapy have an increasing role in the treatment for non-germinoma[5,6]. Because of radiation complications such as neurocognitive deficit[7,8], neuroendocrine dysfunctions[9], and secondary malignancies[10], there has been an attempt to reduce radiation dose and volume. Reduction of treatment volume from craniospinal radiation[11] to whole brain radiation[12], whole ventricular irradiation[13,14], or limited-field irradiation[15] has been reported. Maximal tumor resection combined with chemoradiotherapy[16,17] is another promising option in reducing radiation morbidity and increase long-term overall survival.

The authors reported 82% 5-year overall survival rate for ICGCT treated at the King

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Chulalongkorn Memorial Hospital during 1990-2000[18]. During that time, majority of the treatment was radical radiotherapy especially craniospinal irradiation. Some patients received radiotherapy as therapeutic diagnosis without histopathological proof. After that time, the treatment became multi-modalities with the surgical removal of the tumor and increase use of chemotherapy, while reducing radiation dose and treatment volume. Here, the authors retrospectively reviewed the treatment patterns and overall survival rate of patients treated at the King Chulalongkorn Memorial Hospital in 2001-2008 and compared with a previous study in 1990-2000.

## Material and Method

A descriptive study was established by reviewing patients' records from the Division of Therapeutic Radiology and Oncology, King Chulalongkorn Memorial Hospital. Eligibility criterion was all ICGCT treated between 2001 and 2008. Forty-two patients were included in the present study without selection bias. The results of a previous study[18] were retrieved and presented.

Patient characteristics (age, sex, tumor location, and clinical presentation), investigation (histopathological confirmation, serum tumor markers, and spinal evaluation), and treatments (surgery, chemotherapy, and radiotherapy) were collected from the patients' records. Continuous data was presented in median and range. Categorical data was presented in proportion.

Death of any causes was defined as event. Loss to follow-up was defined as censored. Survival time was from first diagnosis to last follow-up. Survival analysis was evaluated by Kaplan-Meier method. Five-year overall survival rate was reported.

The protocol was approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University.

## Results

### *Patient characteristics*

Forty-two patients were eligible and analyzed. Male predominance (71%) was recorded. The median age was 16 years (range 7-32 years). Pineal region was the most common site in 55%. Interestingly, 12% had synchronous lesions at both pineal and suprasellar regions. Headache was the most common clinical presentation in 60%. Details of patient characteristics of the current study and the previous study are shown in Table 1.

### *Investigation*

Histopathological confirmation, spinal evaluation, and serum tumor markers were increasingly utilized. Out of 41 patients who had histopathological confirmation, 71% were germinoma. Out of 37 patients

**Table 1.** Patient characteristics

| | Year 2001-2008 (42 patients) | Year 1990-2000 (69 patients) |
|---|---|---|
| Age | | |
| Median (range) | 16 (7-32 years) | 5 (2-52 years) |
| Sex | | |
| Male | 30 (71%) | 56 (81%) |
| Female | 12 (29%) | 13 (19%) |
| Tumor location | | |
| Pineal | 18 (43%) | 52 (75%) |
| Pineal and suprasellar | 5 (12%) | 2 (3%) |
| Suprasellar | 10 (24%) | 8 (12%) |
| Basal ganglion | 6 (14%) | 3 (4%) |
| Hypothalamus | 1 (2%) | 3 (4%) |
| Periventricular white matter | 2 (5%) | 1 (2%) |
| Clinical presentation | | |
| Headache or hydrocephalus | 25 (60%) | 59 (86%) |
| Diplopia | 22 (52%) | 40 (58%) |
| Diabetes insipidus | 16 (38%) | 9 (13%) |
| Weakness | 9 (21%) | |
| Hormonal disturbance | 8 (19%) | |

who had MRI spine or CSF cytology, 43% had CNS dissemination. Out of 12 patients who had MRI spine and CSF cytology, 50% had discordant results. Five patients had positive MRI spine with negative CSF cytology. One patient had positive cytology with negative MRI. Elevated beta-human chorionic gonadotropin (B-HCG) and Alfa-fetoprotein (AFP) were discovered in 24% and 16%, respectively. More details of the current study and the previous study are presented in Table 2.

***Treatment***

Reduced dose-volume radiotherapy combined with surgery and chemotherapy was increasingly utilized. Total or partial tumor removal was done in 79% of the patients. Half of the patients received neoadjuvant or adjuvant chemotherapy. Platinum-based regimens were prescribed in the present study and the previous study. Radiotherapy was completed in 91% of the patients. Sixteen patients with CNS dissemination had craniospinal radiation, whereas patients without CNS dissemination had craniospinal radiation, whole brain radiation, whole ventricular radiation, or limited-field irradiation. Details of median radiation dose, dose per fraction, and median treatment time of the current study and the previous study are presented in Table 3.

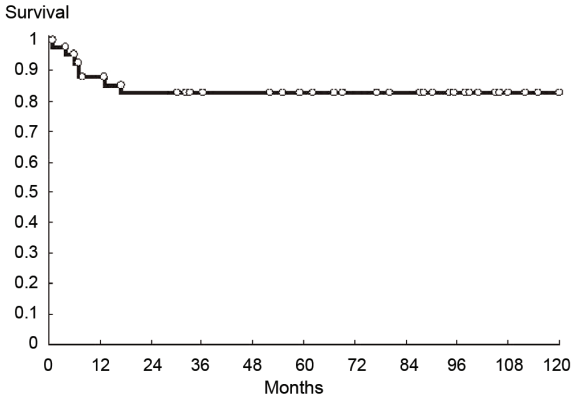


**Fig. 1** Overall survival rate

***Overall survival rate***

Median follow-up time was 65 months (range 1-122 months). Seven out of 42 patients died within 1 to 17 months after first diagnosis and treatment. Three patients died with the disease during radiotherapy courses. Two patients died without disease during adjuvant chemotherapy. Two patients died with recurrent disease after completing treatment. Five-year overall survival rates in all patients were 83% as displayed in Fig. 1, comparable to 82% from the previous study. Survival rates of patients without

**Table 2.** Investigation

| | Year 2001-2008 (42 patients) | Year 1990-2000 (69 patients) |
|---|---|---|
| Investigation | | |
| Histopathological confirmation | 41 (98%) | 42 (61%) |
| Spinal evaluation | 37 (88%) | 13 (19%) |
| Serum tumor markers | 37 (88%) | 46 (67%) |
| Histopathology | | |
| Germinoma | 29 (71%) | 27 (64%) |
| Non-germinoma | 12 (29%) | 15 (36%) |
| Mixed germ cell tumor | 8 | 8 |
| Yolk sac tumor | 3 | |
| Choriocarcinoma | 1 | |
| Embryonal carcinoma | | 1 |
| Teratoma | | 6 |
| Spinal evaluation (CSF cytology, MRI spine) | | |
| Positive | 16 (43%) | 1 (8%) |
| Negative | 21 (57%) | 12 (92%) |
| Serum tumor markers | | |
| Elevated B-HCG > 5 | 9 (24%) | 8 (17%) |
| Range | 8-637 | 7-176 |
| Elevated AFP > 10 | 6 (16%) | 9 (20%) |
| Range | 31-6,126 | 105-20,856 |

**Table 3.** Treatment

| | Year 2001-2008 (42 patients) | Year 1990-2000 (69 patients) |
|---|---|---|
| Surgery | | |
| Total or partial tumor removal | 33 (79%) | 24 (35%) |
| Biopsy | 8 (19%) | 18 (26%) |
| No surgery for histopathology | 1 (2%) | 27 (39%) |
| Chemotherapy | | |
| Neoadjuvant or adjuvant | 21 (50%) | 10 (15%) |
| Radiotherapy | | |
| Completed treatment | 38 (91%) | 62 (90%) |
| With CNS dissemination | | |
| Craniospinal radiation | 16 (100%) | 1 (100%) |
| Without CNS dissemination | | |
| Craniospinal radiation | 5 (23%) | 16 (26%) |
| Whole brain radiation | 10 (45%) | 43 (71%) |
| Whole ventricular radiation | 6 (27%) | - |
| Limited-field radiation | 1 (5%) | 2 (3%) |
| Median radiation dose (Gy) | | |
| Tumor | 54 (46-61.2 Gy) | 54 (50-60 Gy) |
| Brain or Ventricle | 36 (20-43.2 Gy) | 36 (19.5-50 Gy) |
| Spine | 36 (24-45.8 Gy) | 30 (20-44.5 Gy) |
| Dose per fraction (Gy) | | |
| Brain | 1.8-2 | 1.8-2 |
| Spine | 1-2 | 1-2 |
| Median treatment time (days) | 44 | 43 |

CNS dissemination were 88% in this study and 83% in the previous study. Survival rates adjusted for histopathology were 86% for germinoma and 76% for non-germinoma.

**Discussion**

Due to its rarity, randomized studies directly comparing results of different treatment modalities of ICGCT are challenging and therefore have not been successfully performed. Here, the authors reported the results of treating 42 patients with less aggressive radiotherapy combined with surgery and chemotherapy to reduce radiation complication at the King Chulalongkorn Memorial Hospital between 2001 and 2008. The limitations of the study were a retrospective descriptive design and a small number of patients. However, the overall survival rate was comparable to other retrospective studies including the previous report at the King Chulalongkorn Memorial Hospital between 1990 and 2000[18].

The authors found that ICGCT were common in adolescents with a median age of 16 years. Male predominance was recorded. Pineal region was still the most common site for the tumor. Comparing these results with the previous report, synchronous lesions at suprasellar and pineal regions were more commonly seen, 12% versus 3%. This is probably due to the improvement of imaging and increasing use of MRI. All of the patients with synchronous lesions had pure germinoma, which corresponded to other reports that germinoma was the major histopathology in this subgroup[2,19].

From the previous report[18], the percentage of histopathologically confirmed ICGCT had increased and the treatment modalities had changed. Because prognosis is different between each cell type, histopathology is important in selection of treatment protocol. Forty-one out of 42 patients (98%) had histopathological confirmation. Twenty-nine (71%) were germinoma. In the present study, 37 out of 42 patients (88%) had results of serum tumor markers. Majority of the patients (88%) underwent spinal evaluation with MRI spine or CSF cytology or both. Positive MRI spine or CSF cytology were detected in 16 patients (43%). Out of 12 patients who had MRI spine and CSF cytology, 6 (50%) had discordant

results. Other reports showed the discordance of MRI spine and CSF cytology to detect leptomeningeal disease was documented in 14-18% of pediatric medulloblastoma or primitive neuroepithelial tumor[20]. However, continual improved MRI technology will increase the sensitivity, specificity, and accuracy of disease detection. A report revealed that spinal MRI was found to have a greater diagnostic accuracy compared to CSF cytologic analysis in early detection of disseminated medulloblastoma[21]. In addition, delaying spinal MRI and CSF cytologic analysis by more than 2 weeks after surgery can reduce false positive results from both methods. Source of CSF also influences detection rate of leptomeningeal disease. In pediatric brain tumor, lumbar CSF cytology was significantly more sensitive than shunt cytology[22]. However, intracranial CSF cytology may be more sensitive in detecting early stage of dissemination compared to lumbar CSF cytology[23].

In the current study, total or partial tumor removal was attempted in 79% while 19% had tissue biopsy, leaving only 2% with unknown histopathology. In the previous report, during 1990 to 2000, 39% did not have tissue diagnosis[18]. Therefore, management was defined more accurately because more patients had histopathology and extent of disease.

Higher number of patients received systemic chemotherapy, 50% in the current versus 15% in the previous study. Chemotherapy was platinum-based containing regimen. Several reports have confirmed the efficacy of combining chemotherapy with radiation therapy to improve treatment outcome. In addition, the objective was to reduce radiation treatment volume and dose in pediatric cases to reduce treatment complications[2,17,24,25]. Systemic chemotherapy alone is not yet recommended as a standard treatment for this disease[26].

Radiation treatment volume and dose in ICGCT remains controversial. Traditionally, cranio-spinal radiation was utilized in these patients because there are chances of CNS dissemination. However, several studies showed that with the addition of chemotherapy, the volume and dose of radiation treatment can be reduced and is a reasonable option in curing this disease. Moreover, additional chemotherapy has improved survival rates in ICGCT, especially in those with non-germinomatous germ cell tumor because they are less radiosensitive. Recently, craniospinal radiation is still recommended in patients diagnosed with leptomeningeal disease[2,16,17,25]. In non-disseminated disease, radiation treatment volume could be either whole brain, whole ventricular, or limited-field radiation. Report of pattern of relapse from French (SFOP experience) in non-metastatic germinoma treated with chemotherapy and limited-field radiation suggested that whole ventricular radiation could reduce disease relapse[27].

In the past, management of ICGCT depended on histopathology whether it was germinoma or non-germinoma. Matsutani et al proposed classifying ICGCT into three prognostic groups: good, intermediate, and poor[3]. Non-germinomatous germ cell tumors are relatively resistant to radiation therapy and chemotherapy. With a 5-year overall survival ranged from 30-50%, Non-germinomatous germ cell tumors have a poorer prognosis than germinoma[2,3,28]. Moreover, treatments adjusted to risk can affect prognoses. Kanamori et al. reported a retrospective review of 108 intracranial germ cell patients. Treatment was risk adjusted to the prognostic group. The good prognostic group was treated with chemotherapy and reduced-dose whole ventricular radiation whereas chemoradiation combined with radical resection were applied to the intermediate and poor risk groups. In the intermediate risk group, the ten-year overall survival rate and progression-free survival rate were 100% and 93%, respectively. In the poor prognosis group, 5-year overall survival rate and progression-free survival rate were 56% and 29%, respectively[2].

In the present study, 91% of the patients had completed radiation treatment as planned. Radiation treatment volume was tailored to the extent of disease because most of the patients had spinal evaluation before starting treatment. Craniospinal radiation was applied in every patient who had positive spinal MRI or CSF cytology. Increasing utilization of whole ventricular radiation, while decreasing use of craniospinal radiation, has been documented in patients with negative leptomeningeal disease. There was only one patient treated with limited-field radiation. With median follow-up time of 65 months, a 5-year overall survival rates in all patients were 83%, comparable to 82% from the previous study. Survival rates of patients without CNS dissemination were 88% in the present study and 83% in the previous study. Survival rates adjusted for histopathology were 86% for germinoma and 76% for non-germinoma.

**Conclusion**

Management of ICGCT should be risk-adjusted. Spinal evaluation with MRI spine and CSF cytology are important. Combined chemoradiation

with reduced radiation treatment volume is a feasible option for these patients.

**Potential conflicts of interest**

None.

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## *การรักษามะเร็งสมองชนิดเยอร์มเซลล์ที่ในโรงพยาบาลจุฬาลงกรณ์*

***ทัศน์พงศ์ รายยวา, ชลเกียรติ ขอประเสริฐ, ชวลิต เลิศบุษยานุกูล, ปัญญา เสกสรรค์, ดารินทร์ ซอโสตถิกุล, จิระพร อมรฟ้า, กาญจนา โชติเลอศักดิ์***

***วัตถุประสงค์:*** *เพื่อศึกษาผลการรักษามะเร็งสมองชนิดเยอร์มเซลล์ในโรงพยาบาลจุฬาลงกรณ์ ด้วยการฉายรังสีปริมาณลดลงร่วมกับการผ่าตัดและเคมีบำบัด เพื่อลดผลข้างเคียงจากการฉายรังสี*

***วัสดุและวิธีการ:*** *การศึกษาแบบพรรณนาโดยรวบรวมข้อมูลผู้ป่วยจากสาขารังสีรักษาและมะเร็งวิทยาในปี พ.ศ. 2544-2551 และเปรียบเทียบกับผลการศึกษาในปี พ.ศ. 2533-2543 โดยติดตามผลการรักษา 65 เดือน สรุปคุณลักษณะผู้ป่วย การตรวจวินิจฉัยโรค และวิธีการรักษาด้วยค่าสัดส่วน สรุปอัตราการรอดชีวิตด้วยวิธี Kaplan-Meier*

***ผลการศึกษา:*** *ผู้ป่วยทั้งสิ้น 42 ราย เป็นเพศชายร้อยละ 71 อายุเฉลี่ย 16 ปี พบมะเร็งบริเวณต่อมไพเนียลมากที่สุดถึงร้อยละ 55 โดยร้อยละ 12 จะพบมะเร็งบริเวณต่อมใต้สมองร่วมด้วย การตรวจผลชิ้นเนื้อพบ Germinoma ร้อยละ 71 จากผู้ป่วย 41 ราย การตรวจภาพเอกซเรย์คลื่นแม่เหล็กหรือเจาะตรวจน้ำไขสันหลัง พบการกระจายบริเวณระบบประสาทส่วนกลางร้อยละ 43 จากผู้ป่วย 37 ราย การลดปริมาณรังสีลงเพื่อลดผลข้างเคียงจากรังสีโดยรักษาร่วมกับการผ่าตัดและเคมีบำบัดเป็นที่นิยมมากขึ้น อัตราการรอดชีวิตที่ 5 ปี ร้อยละ 83 จากการศึกษานี้เทียบกับร้อยละ 82 จากการศึกษาปี พ.ศ. 2533-2543 และกรณีที่ไม่มีการกระจายบริเวณระบบประสาทส่วนกลางจะพบอัตราการรอดชีวิตสูงถึงร้อยละ 88 และ 83 ตามลำดับ ถ้าแบ่งตามผลพยาธิวิทยาจะพบอัตราการรอดชีวิตร้อยละ 86 ใน Germinoma และร้อยละ 76 ใน Non-germinoma*

***สรุป:*** *วิธีการฉายรังสีปริมาณลดลงร่วมกับการผ่าตัดและเคมีบำบัดเพื่อลดผลข้างเคียงจากการฉายรังสี เป็นวิธีการรักษามะเร็งสมองชนิดเยอร์มเซลล์ที่มีประสิทธิภาพดี*