

## 두개강내 배아종의 방사선 치료

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### Radiation Therapy of Intracranial Germinoma

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**Purpose** : Intracranial germinoma is the most radiocurable tumor of the primary intracranial neoplasm. But, the optimum radiation dose and target volume remain controversial. In this retrospective study, we analysed the spreading pattern at presentation and the pattern of the failure and survival of intracranial germinoma.

**Materials and Methods** : From 1989 to 1996, 23 patients were treated for intracranial germinoma at Department of Radiation Oncology. Twenty-one patients were treated at their initial presentation and 2 patients were treated for recurrent disease. Six patients had multiple tumor masses on MRI and 7 patients had ventricular seeding on MRI. The examination of cerebrospinal fluid cytology was done in 15 patients and 3 out of 15 patients had positive cerebrospinal cytology. In tumor marker study of  $\alpha$ -FP and  $\beta$ -hCG, 6 patients had mildly elevated  $\beta$ -hCG in serum or cerebrospinal fluid. Twenty-one patients were treated with whole craniospinal axis irradiation and 2 patients were given whole ventricular radiation therapy. The total dose was ranged between 4500cGy and 5600cGy to primary tumor site (median 5580 cGy). Dose to the entire ventricular system ranged from 1980cGy to 3960 cGy (median 2700cGy) and dose to the spinal axis ranged from 2160cGy to 3900cGy (median 2700cGy).

**Results** : Of 23 patients, 21 patients are alive without evidence of disease for median 4 years follow-up. One patient who had markedly elevated  $\alpha$ -FP and  $\beta$ -hCG suffered from persistent disease after radiation therapy and received 2 cycles of chemotherapy. She died 9 months after chemotherapy. One patient who developed ventricular seeding after gamma-knife was treated with whole craniospinal irradiation, he died after 1 year due to probably brain necrosis. The hematologic toxicity of 3 or 4 grade were seen in 7 patients, and patient's endocrinologic dysfunction was not deteriorated after radiation therapy. One patient had been treated with growth hormone replacement due to short stature.

**Conclusions :** This retrospective study has confirmed the excellent result of radiation therapy in intracranial germinoma. The complication rate during or after radiation therapy is considered within acceptable range. It is necessary to further investigate the optimal dose and treatment volume of radiation therapy. The role of chemotherapy in the treatment of intracranial germinoma should be further investigated.

**Key Words :** Germinoma, Radiation therapy, Craniospinal irradiation

## INTRODUCTION

Intracranial germinoma is the most radiosensitive tumor of the primary intracranial neoplasm. This tumor constitute 0.4% to 9.4% of childhood brain tumors<sup>1-3</sup>. They are more common in the Far East where they account for 2.5% of all intracranial neoplasms<sup>4</sup>.

The sex incidence varies, with tumors in pineal gland occurring predominantly in males whereas tumors in suprasellar region have a predominantly female sex distribution<sup>5</sup>. Intracranial germinoma occurs frequently in the pineal gland, in the suprasellar region, basal ganglia and thalamus. They tend to spread through the cerebrospinal axis, but the incidence of spinal axis seeding has not been well established.

The optimum management of intracranial germinoma is unclear. Tissue diagnosis is of critical importance in the treatment of intracranial germinoma. In the past, attempt of biopsy or resection of intracranial germinoma were associated with a high morbidity as high as 50%<sup>5-8</sup>. But microsurgical techniques and stereotactic biopsy have reduced morbidity to 0-5%<sup>9, 10</sup>.

Radiation therapy has proven to be effective as primary treatment of germinoma, but the optimal dose and treatment volume and indications for irradiation of the entire cerebrospinal axis have not been clearly established<sup>1-3, 11, 12</sup>.

In this retrospective study, we analysed the spreading pattern at presentation, the pattern of the failure, survival and complication of radiotherapy in intracranial germinoma.

## METHODS AND MATERIALS

From 1989 to 1996, Twenty-three patients were treated for intracranial germinoma at the Department of Radiation Oncology. Twenty-one patients were treated at their initial presentation and 2 patients were treated for recurrent disease.

The patients' age ranged from 8 to 49 years with a median of 14 years. There were 15 males and 8 females. Histologic diagnosis was obtained in 19 out of 23 cases: 9 by open or stereotactic biopsy, 10 by surgical resection. The presumptive diagnosis of germinoma in unbiopsied patients was based on clinical finding, laboratory and radiologic studies including CT or MRI or tumor marker study. All patients have been followed for a minimum of 1 year with a range from 1 year to 7 years (median 4 years). Follow-up data were calculated from the date of diagnosis. The morbidity associated with the disease and its treatment is estimated by retrospective chart review and telephone interview.

The location of the tumor and its spreading pattern at initial presentation were described at Table 1. In 9 patients, tumors were confined to a single site within either the pineal region (5) or the suprasellar region (2) or basal ganglia region (2). Six patients showed multiple tumor masses on MRI and 7 patients showed ventricular seeding on MRI. Three patients showed meningeal seeding on MRI. The analysis of cerebrospinal fluid (CSF) cytology was done in 15 patients and 3 patients had positive CSF cytology.

In tumor marker study of  $\alpha$ -fetoprotein ( $\alpha$ -FP) and  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG), 1

**Table 1. Location and Spread Patterns of the Tumor**

Site	Sex		ventricular seeding or extension on MRI	meningeal seeding on MRI	positive CSF cytology	lesion confined to 1 site
	male	female				
pineal gland	11* <sup>†</sup>	2	4	3	2	5
suprasellar area	4	6	3	0	1	2
basal ganglia	3	1 <sup>‡</sup>	0	0	0	2

\* : three patients had pineal and suprasellar mass  
 † : one patient had pineal and cerebropontine angle mass  
 ‡ : she had pineal and basal ganglia mass

**Table 2. Study of  $\alpha$ -FP and  $\beta$ -hCG**

Site	No. of cases	$\alpha$ -FP >3ng/ml	$\beta$ -hCG >3mIU/ml
serum	23	1*	7*
CSF	11	0	3

\* :  $\alpha$ -FP and  $\beta$ -hCG of this patient were 57.9ng/ml and 31270mIU/ml

patient had markedly elevated  $\alpha$ -FP and  $\beta$ -hCG (Table 2). She showed suprasellar mass with extension to hypothalamus. Suprasellar mass was confirmed to be a germinoma by biopsy, but biopsy of hypothalamic lesion was not done. Therefore, we cannot exclude the possibility of mixed germ cell tumor. Other 6 patients had mildly elevated  $\beta$ -hCG in serum or CSF (4.1–37.3mIU/ml).

Radiation therapy was given with 4MV X-ray of a linear accelerator. Two patients were given whole ventricular radiation therapy at initial presentation. These patients were treated without biopsy. For presumptive diagnosis of germinoma, radiologic study was done to confirm the responsibility of tumor after 24Gy of radiotherapy. These patients achieved more than partial response. Nineteen patients were treated with whole craniospinal axis irradiation therapy at initial presentation. There were 18 biopsy-proven germinoma and 1 biopsy-unproven germinoma in this group. One patient who was treated initially with whole ventricular radiation therapy (5400cGy to tumor mass, 3960cGy to whole ventricle) at another hospital recurred in the spinal axis after 3 years 5 months. He was treated with whole craniospinal

axis radiation therapy (1080cGy to whole brain, 3600cGy to whole spine, 4500cGy to recurred mass) at our hospital. One patient who failed to gamma-knife (22Gy to 50% isodose line) was retreated with whole craniospinal axis irradiation (5460cGy to tumor mass, 2160cGy to spine). A total dose was ranged between 4500 and 5600cGy to primary tumor site (median 5580cGy). Dose to the entire ventricular system ranged from 1980cGy to 3960cGy (median 2700cGy) and dose to the spinal axis ranged from 2160cGy to 3900cGy (median 2700cGy).

Two patients were treated with chemotherapy. One patient with highly elevated  $\alpha$ -FP and  $\beta$ -hCG showed partial response after radiation therapy. She was treated with 2 cycles of 8 drugs in 1 day chemotherapy at Department of Pediatric Oncology. Another one patient was treated with 2 cycles of EP (VP-16 and CDDP) chemotherapy before radiotherapy. He showed partial response after chemotherapy and then he was treated with whole craniospinal axis irradiation.

## RESULTS

Of the 21 patients who were treated at our department initially, 20 patients are alive without any evidence of disease with a median follow-up of 4 years. One patient who had markedly elevated  $\alpha$ -FP and  $\beta$ -hCG suffered from persistent disease after radiation therapy and received 2 cycles of chemotherapy. She died at 9 months after chemotherapy due to tumor progression. One patient who developed recurrence in the spinal axis in 3 years 5 months after the whole ven-

tricular irradiation at another hospital was retreated with whole craniospinal axis irradiation, and he is now alive at 4 years without any evidence of disease. One patient who developed ventricular seeding and increased primary mass after gamma-knife was retreated with whole craniospinal irradiation (5460cGy to tumor mass, 2160cGy to spine) and he died 1 year after retreatment. Brain MRI showed abnormal findings suspected to radiation change or enlarging tumor. This lesion was interpreted to radiation necrosis on Tallium-201 brain SPECT.

Table 3 shows hematologic toxicity of whole craniospinal irradiation. None of these patients was suffered from infectious disease during radiation therapy and none of these patients had treatment delay due to neutropenia.

Twelve patients out of 23 patients developed endocrinologic dysfunction prior to radiation therapy and this problem was not deteriorated after radiation therapy. Among 12 patients aged below 17 years who were treated with whole craniospinal axis irradiation, growth retardation below 25 percentiles was seen in 1 patient. This patient was presented with panhypopituitarism at initial diagnosis. His age was 16 years old. In this patient, tumor mass were located in sella, suprasella, pineal gland and third ventricle on MRI. This patient's height was below 3 percentile at initial presentation. He received whole craniospinal axis irradiation (primary site 5500cGy, spinal axis 2700cGy). He has been treated with growth hormone replacement for 4 years. He is 20 years old, and his height is 158cm at present (below 3 percentile). We suspect his growth delay to be combined effect of radiation therapy and growth

hormone deficiency.

## DISCUSSION

This retrospective study has confirmed the excellent result by radiation therapy in the treatment for intracranial germinomas. Similar results have been reported by other study<sup>12-16</sup>. But radiation dose and target volume remain controversial for optimum treatment of intracranial germinoma.

A radiation dose of 45-55Gy has been commonly used. This dose is usually tolerable for normal brain tissue<sup>17</sup>. However, there is some question to whether as much radiation as 45-55 Gy is really necessary to cure this radiosensitive tumor, since testicular seminoma (histologically identical to intracranial germinoma) has been treated successfully with 25-35Gy of radiation. Sung et al reported that local control improves from 47% with 40Gy or less to 90% with 50Gy or more<sup>18</sup>. Wara et al obtained similar results for patients receiving lesser than 4500cGy compared with those receiving more than 45Gy<sup>11</sup>. Jenkin et al reviewed 21 pineal gland germinoma (16 biopsy proven, 2 biopsy non-diagnostic, and 3 metastasis unbiopsied patients)<sup>19</sup>. Radiation dose to the primary tumor was 4000-4500cGy in 4/19 (22%), 50-55Gy in 15/19 (77%), no patient with a verified germinoma relapsed in-field after irradiation. Shibamoto reported his result of dose reduction study for intracranial germinoma, together with the long term outcome in the patients previously given higher doses<sup>8</sup>. In his report, the patients were divided into 3 groups according to the dose to the primary tumor, 48-52.5Gy, 54-62Gy, 18.7-47.0Gy. 10 year relapse free survival rates were the corresponding to 88%, 92%, 77% and p value was 0.53. Shibamoto reported that evident recent memory disturbance developed in 2 of the 17 patients who had received dose of 54Gy or more and in 2 of the 20 patients who received 50±2Gy. In contrast, none of the 26 patients who received dose of 47Gy or less developed memory disturbance. Two patients who received 40Gy and 50Gy developed some degree of pituitary dysfunction

**Table 3. Hematologic Toxicity of WCSI\***

RTOG grade	WBC count	No. of patients
0	>4000	1
1	3000-4000	3
2	2000-3000	10
3	1000-2000	5
4	<1000	2

\* : Whole craniospinal axis irradiation

after radiotherapy and none of the patients receiving lower dose developed any endocrinologic dysfunction. Doses of 45 to 50Gy given in 1.8Gy fractions will usually depress growth hormone first<sup>20</sup>. Adrenocorticotrophic hormone and gonadotropins are depressed later. Thyroid-stimulating hormone is the last to decrease. Endocrinologic dysfunction may require 1 to 10 years or more to develop. In children, the response of the hypothalamic-pituitary axis follows the same general sequence found in the adult with their exception : 1) the responses appear at lower dose (growth hormone reduction appears after 20 to 30Gy) 2) the latent period to response is shorter<sup>21</sup>. In our study, no patient had deteriorated endocrinologic dysfunction after radiation therapy with median follow-up of 4 years. Further follow-up is needed.

The radiation field necessary for optimal treatment continue to be debated. Autopsy series demonstrate a significant tendency of intracranial germinoma to spread along the ventricular system and implant in a subependymal location in contiguous and noncontiguous fashion<sup>1, 22</sup>. The reported incidence of malignant cells in the CSF varies between 0–55%<sup>2, 3, 5, 11, 15, 23</sup>. In our series, it occurred in 3 out of 15 cases and incidence of leptomeningeal extension or seeding on MRI was 38%(8/21).

The use of prophylactic spinal axis irradiation to treat intracranial germinoma is controversial. Sung et al reported that in 14 patients with biopsy-proven germinoma treated without spinal irradiation, 6 patients eventually developed spinal metastasis<sup>18</sup>. Jenkin et al reported that in 5 patients treated without spinal radiotherapy, 2 patients later failed in the spine<sup>3</sup>. However, some series have shown good results without spinal irradiation. Shibamoto et al reported that none of 6 patients with positive CSF cytology developed spinal axis metastasis despite local radiotherapy alone<sup>11</sup>. Linstadt et al reported that only one of the 31 patients treated without adjuvant spinal axis irradiation developed spinal metastasis<sup>15</sup>. They reviewed the results of treatment for germinoma with or without spinal irradiation for histologically verified

tumors and the incidence of spinal failure was 8% versus 23% respectively. But for unverified tumors, 11% versus 9% respectively. In our study, all patients who were treated at initial presentation in our department did not developed spinal failure. At present, the indications for spinal irradiation are not clear. Multiple foci of tumor, ventricular or meningeal seeding, tumor spillage at surgery, and positive CSF cytology have been suggested as risk factor for spinal axis metastasis<sup>1, 11, 13, 15, 18, 24</sup>. There was no randomized study about this issue, but we agree this policy.

Systemic chemotherapy is presently being investigated for intracranial germinoma<sup>25-28</sup>. Several clinical trials have confirmed that CNS germinoma are highly responsive to chemotherapy such as CDDP, VP-16, carboplatin<sup>25-28</sup>. But chemotherapy is associated with unacceptably high recurrence rate in many reports and long term toxicity is still unclear<sup>28-30</sup>. Shibamoto et al reported that 3 patients received chemotherapy containing CDDP and VP-16 and all patients developed recurrence<sup>30</sup>. Balmaceda reported a therapeutic trial to determine whether irradiation could be avoided<sup>28</sup>. In his study, induction chemotherapy consisted of four cycles of carboplatin, etoposide, bleomycin. Seventy-eight percent of patients (55 of 71 patients) achieved a complete response with six cycles of chemotherapy and no irradiation. Despite achievement of a complete response, tumor has recurred in 28 patients to date. The leptomeningeal recurrences developed in approximately 50% of patients. Irradiation may lead to long-term sequelae including intellectual deterioration, growth retardation, endocrine dysfunction and these complication are dose-dependent<sup>17</sup>. Chemotherapy has recently been advocated as an adjuvant therapy with the radiation therapy to decrease the late complication of high dose radiation by lowering the total dose of radiation<sup>27</sup>. Allen et al reported the result of the neoadjuvant chemotherapy with the radiation therapy<sup>27</sup>. Depending on the responding to the neoadjuvant chemotherapy consist of 2 courses of carboplatin, radiation dose was modified. Patients

experiencing a complete response received 3060 cGy to the primary site with or without 2160cGy craniospinal axis irradiation. Patients with less than a complete response received 5040cGy to the primary site with or without 3060cGy craniospinal axis irradiation. They reported that 10 of 11 patients are alive and remain in continuous remission with a median follow-up of 25 months.

In conclusion, intracranial germinoma has high cure rate with radiation therapy. And it is necessary to determine optimal dose and treatment volume of radiotherapy. Role of chemotherapy in treatment of intracranial germinoma should be further investigated.

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= 국문 초록 =

두개강내 배아종의 방사선 치료

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**목 적 :** 두개내 배아종은 방사선 치료로 완치율이 높은 종양이나 현재까지 적절한 방사선 조사량이나 조사 범위에 대한 원칙은 확립되지 않은 상태이다. 본 저자는 본원에서 방사선 치료를 시행한 환자들의 치료 성적과 재발 양상을 알고자 후향적 분석을 하였다.

**대상 및 방법 :** 1989년에서 1996년까지 방사선 치료를 시행한 23명의 환자를 대상으로 하였다. 이 중 21명은 처음 진단시 본과에서 방사선 치료를 하였고 나머지 2명은 재발 뒤 본과에서 방사선 치료를 받았다. 자기공명영상상 6명에서 다발성종괴가 관찰되었고 7명에서 뇌실 내 전이 소견이 보였다. 뇌척추액검사를 시행한 15명중 3명에서 종양 세포가 관찰되었다. 종양지표검사상 6명에서 혈장이나 뇌척추액의 베타 음모성선자극 호르몬의 수치가 다소 상승되어 있었다. 21명은 전 뇌척수조사를 받았고 2명은 전뇌실조사를 받았다.

**결 과 :** 23명 중 21명은 현재 중앙 추적 기간 4 년 시점에서 무병 상태로 관찰되고 있다. 치료 중 백혈구 감소가 3 또는 4단계인 환자는 7명이었고 방사선조사후 내분비 상태가 악화된 환자는 없었다. 전뇌척수조사를 받은 환자중 1명이 저신장으로 성장 호르몬 치료를 받고 있다.

**결 론 :** 본원에서 치료한 두개내 배아종은 기존의 보고와 마찬가지로 높은 관해율을 보이고 있다. 치료 중이나 치료 후의 부작용의 정도와 빈도는 현시점에서 허용 범위에 있는 것으로 생각되었다. 두개내 배아종의 방사선 조사량과 조사 범위, 약물 치료에 관해서는 좀 더 연구가 필요할 것으로 생각된다.