Intracranial Germ Cell Tumors : Experience in King Chulalongkorn Memorial Hospital

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Abstract

A retrospective study was performed on 69 patients with intracranial germ cell tumors who were treated at the Division of Radiation Oncology, Department of Radiology, King Chulalongkorn Memorial Hospital from 1990 to 2000. Median age was 15 years. Forty-two cases (60.87%) had histologically confirmed germinoma or nongerminomatous germ cell tumors. Germinoma was the predominate histology followed by mixed germ cell tumors. Pineal and suprasellar regions were the two leading sites, hydrocephalus (85.5%) and diplopia (57.97%) were the two most common clinical presentations. Only 13 cases had the result of cerebrospinal fluid (CSF) cytology or magnetic resonance imagine (MRI) of the spine before initial treatment. Serum tumor markers, Alpha fetoprotein and β-human chorionic gonadotropin, were available in 66.67 per cent. Total or partial tumor removal were feasible in 24 cases. Whole brain irradiation was given in almost all cases with the median dose of 3,600 cGy. The median total tumor dose was 5,400 cGy. Whole spine radiation was utilized in 17 cases. The mean follow-up time was 41 months. The five-year disease free survival was 73.59 per cent. Overall 3 and 5 year survival rates were 86.45 per cent and 81.64 per cent, respectively.

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Intracranial germ cell tumors are relatively rare primary central nervous system tumors. They occur mostly in children and young adults. Their most common locations are the pineal gland and suprasellar regions[1]. Because of the morbidity of the surgical approach in these areas, the exact incidences of specific histopathological types of germ cell tumors are difficult to determine; the prognosis depends not only on the extent of disease at presentation but also the histopathology. For instance, germinoma has a better prognosis than non-germinoma[2-4]. The management of intracranial germ cell tumors remain unsettled. Radiation therapy has been played an important part in the treatment of intracranial germ cell tumors. Recently, there was an attempt to utilize chemotherapy to improve survival and to decrease the dose or volume of radiation therapy. The authors retrospectively reviewed the demographic and clinical characteristics including treatment and natural course of patients with primary intracranial germ cell tumors.

MATERIAL AND METHOD

All records of patients with intracranial germ cell tumors treated at the Radiation Oncology Division, King Chulalongkorn Memorial Hospital between 1990 and 2000 were retrospectively reviewed. The diagnosis of intracranial germ cell tumors was made either by histopathology of the surgical biopsied specimens or the early response to radiation treatment of the pineal region tumors on computed tomography (CT) or MRI. Patient characteristics, types of treatment and survival were analyzed.

Overall survival (OS) time was defined as the duration from the diagnosis (surgery or imaging) to the date of last follow-up or death. Disease free survival (DFS) time was measured from the time of complete treatment to the date of diagnosis of recurrent disease or last follow-up. Survival analysis was calculated using the method of Kaplan and Meier.

RESULTS

Sixty-nine patients were diagnosed with primary intracranial germ cell tumors. Forty-two cases had histological confirmed germinoma or non-germinoma germ cell tumors. The other 27 cases were diagnosed with pineal region tumor on CT or MRI with the early response to radiation therapy. Patient characteristics are summarized in Table 1.

At the time of diagnosis, lumbar puncture for CSF cytology or MRI of the spine were performed in 13 cases for assessing spinal cord metastasis, which was found in one case, a 2-year-old boy, by MRI of the spine. Forty-six cases (66.67%) had results of serum β-human chorionic gonadotropin (β-HCG), Alfa-fetoprotein (AFP) or both. Eight cases had minimal rising of β-HCG, 7.1-176.2 mu/ml (normal < 5 mu/ml), whereas 9 cases had elevated alfa-fetoprotein levels, 105.4-20856 IU/ml (normal < 10 IU/ml). Of the 42 cases with histopathologically confirmed germ cell tumors, twenty-seven cases were pure germinona. Details of pathology are shown in Table 2.

Table 1. Patient characteristics.

	Cases	%
Age		
Median (Range)	15 years (2-52years)	
Sex		
Male	56	81.16
Female	13	18.84
Tumor location		
Pineal region	52	75.36
Suprasellar	8	11.59
Synchronous Pineal and suprasellar	2	2.9
Basal ganglion and thalamus	3	4.3
Hypothalamus	3	4.3
Periventricular white matter	1	1.45
Clinical presentation		
Headache or Hydrocephalus	59	85.5
Diplopia	40	57.97
Diabetes insipidus	9	13

Treatment

Of 69 patients, 63 received surgical intervention. Twenty-four patients underwent total or partial tumor removal and the rest had ventriculo-peritoneal shunt or biopsy. Sixty-eight patients received post-operative radiation therapy. The one who was not given the radiation treatment was due to benign histopathology which was a mature cystic teratoma. Radiation treatment was completed as planned in 62 cases (91.2%). Whole brain radiation was given in 60 cases. Two cases received only limited field radiation. Whole spine radiation was utilized in 17 cases.

Radiation dose was analyzed in patients who completed the treatment as planned. All patients were treated using a Co-60 machine or 6MV Linac. The brain was treated with opposing lateral fields with 1.8-2 Gy per fraction per day. Whole spine field was treated posteriorly down to S2-S3 with 1-2 Gy per fraction per day depending upon patient age and performance status. Median whole brain and primary tumor doses in 61 cases were 3,600 cGy and 5,400 cGy, respectively. Median treatment time was 43 days (6 weeks). Median whole spine dose was 3,000 cGy in 33 days (4.5 weeks). The radiation doses are summarized in Table 3. Ten cases received neoadjuvant or adjuvant chemotherapy which was VAC (Vincristine, Adriamycin, Cyclophosphamide), BEP (Bleomycin, Etoposide, Platinum), or PVB (Platinum, Vinblastine, Bleomycin) regimens.

Disease free survival (DFS) and overall survival (OS)

Of 62 cases who received complete treatment, 57 had adequate information for assessing patient status. The mean follow-up time was 41 months. Four cases had local recurrence in the brain. Nine patients had spinal metastasis, including the one who had spinal disease at the time of diagnosis. For 8 patients who had spinal relapse after complete treatement, one case had prophylactic spinal radiation in the initial treatment. The rest, 7 cases, did not get spinal RT. In 16 cases who had spinal radiation for prophylaxis, one patient had spinal relapse after treatment.

Of 69 cases, 62 cases had complete treatment as planned. Five patients did not have enough information to assess the patient status at last follow-up. Consequently, survival analysis was obtained in 57 cases. The five-year diasease free survival was 73.59 per cent (Fig. 1). Overall 3 and 5 year survival were 86.45 per cent and 81.64 per cent respectively (Fig. 2).

Table 2. Pathological classification of cases with intracranial germ cell tumors.

Histopathology	Number of patients	%
Histopathological proved	42	
Germinoma	27	64.29
Mixed germ cell tumor	7	16.67
Immature teratoma	5	11.9
Mature teratoma	1	2.38
Embryonal cell carcinoma	1	2.38
Non-germinoma	1	2.38
No histology	27	

DISCUSSION

Intracranial germ cell tumors are relatively rare primary central nervous system tumors, accounting for 0.1-3.4 per cent of all intracranial tumors[5]. The incidence varies geographically, more common in Eastern than Western series[2,3]. The average incidence in Chulalongkorn Memorial Hospital was 3.8 per cent of primary central nervous system (CNS) tumors per year[6]. Prognosis has apparently been correlated with histological classification. Pure germinoma has a much better outcome than non-germinomatous germ cell tumors[2-4]. More than 90 per cent 5-year survival rate has been reported in patients with germinoma[2,7,8]. Poorer outcome has been shown in non-germinoma patients, whose reported survival

Table 3. Radiation dose.

RT techniques	Complete treatment (Cases)	Median dose (Range)	Median treatment time
Whole brain	60	3,600 cGy (1950-5000 cGy)	-
Total tumor dose	62	5,400 cGy (5,000-6,000 cGy)	43 days
Spine dose	17	3,000 cGy (2,000-4,450 cGy)	33 days

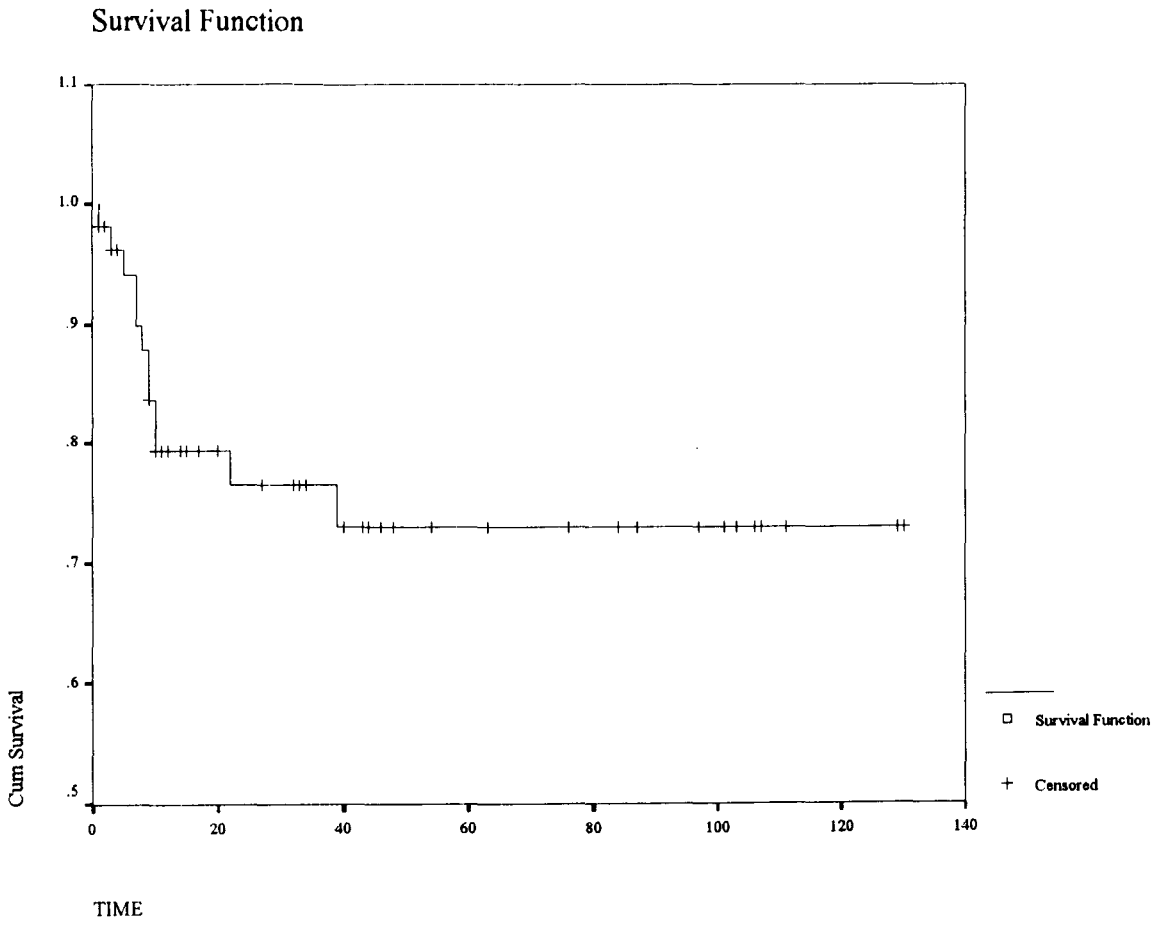

Fig. 1. Disease free survival curve.

rates vary between 30-70 per cent. Mature teratoma has a relatively favorable outcome[2,4,7-9].

Median age of the presented patients was 15 years old. Seventy-eight per cent of the patients were younger than 20 years old. These findings are consistent with previous reports which found that intracranial germ cell tumors are found in young adults or childhood and the peak incidence is in the second decade[1]. In the present study, the disease was more common in males, 81.16 per cent. Pineal and suprasellar regions were the two leading sites, preferable in the pineal region. The authors had 2 patients with synchronous lesions, accounting for 2.9 per cent of all patients. One of them was diagnosed histologically as immature teratoma. The other case did not have tissue biopsy. Synchronous lesions in the pineal and suprasellar areas were found 5-10 per cent[7] Germinoma is the predominate histology in this subgroup [2]. In a report from Japan, they found 6 cases with synchronous germ cell tumors were found in the pineal and suprasellar regions, accounting for 12.8 per cent of all germ cell tumors. In all cases, the initial symptoms were attributable to the suprasellar lesion. Five of the six cases were diagnosed as germinoma[10].

Basal ganglion and the thalamus are other regions of the brain where intracranial germ cell tumor may occur. There were 3 cases with basal ganglion and thalamus lesions and 3 cases in the hypothalamus in the present study. Five of the six cases were histologically proved germinoma. One of the patients with a hypothalamic lesion had mixed germinoma, immature teratoma and a yolk sac tumor. Of note, there

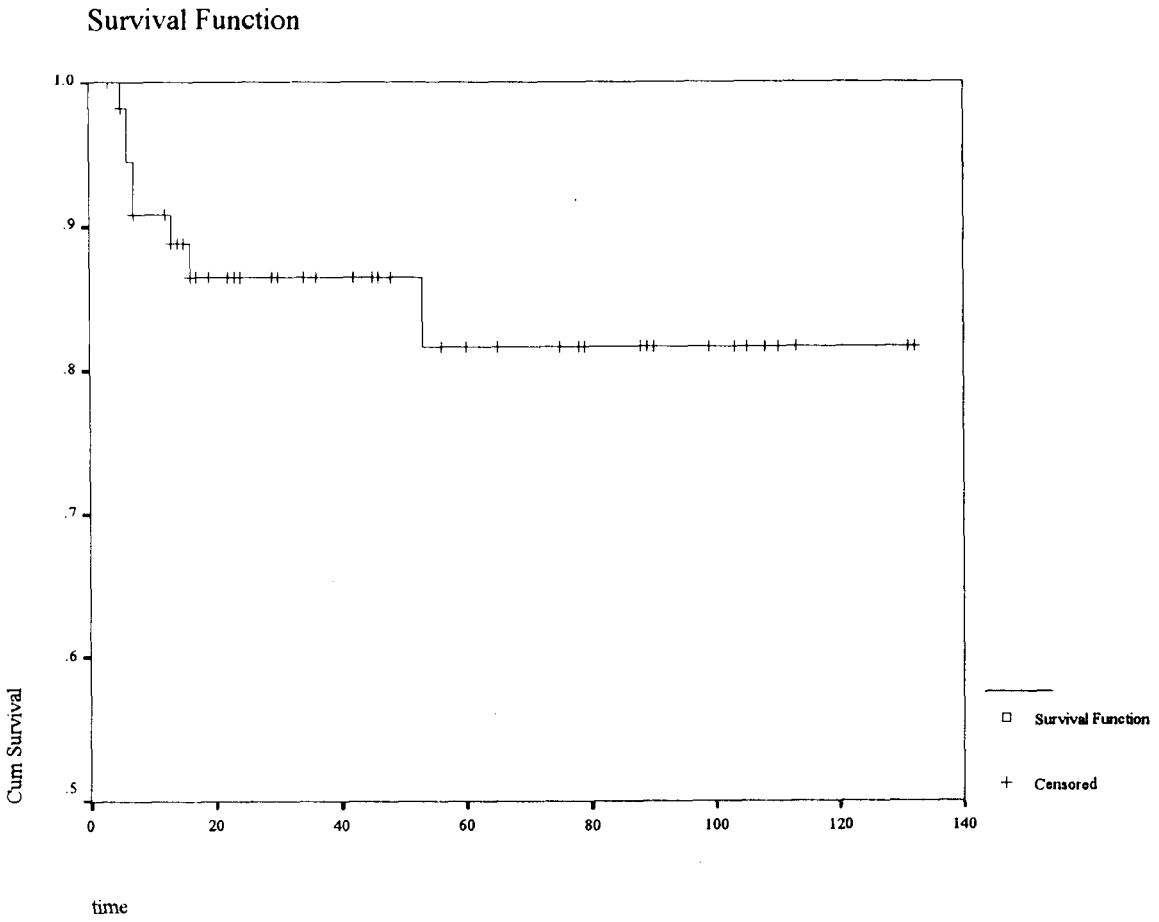

Fig. 2. Overall survival curve.

was a patient who had multiple enhancing lesions distributed in the brain, at the periventricular white matter and corpus collosum. Histological diagnosis was germinoma. CSF cytology was negative.

Clinical presentations of intracranial germ cell tumors depend on the tumor location, tumor size and extension. The majority of tumors (75.36%) in the present study occured in the pineal region. Therefore, hydrocephalus and diplopia were the most common clinical presentations. Diabetes insipidus is the classic symptom and sign of suprasellar and hypothalamic lesions.

Histological diagnosis is usually required in intracranial tumors. However, the morbidity of the surgical approaches in these areas is a limitation. In the past, radiation treatment was used without histological confirmation. Response to low dose radiation, along with measurement of serum tumor marker provides diagnostic information[1]. CT characteristics may allow differentiation of benign tumors from malignant germ cell lesions. MRI can provide excellent anatomic detail of pineal region tumors. However, MRI signal characteristics are usually non-specific [11,12]. Nowadays, biopsy or tumor resection are more commonly attempted.

In the present review, total or partial tumor removal were feasible in 24 cases. Thirty nine cases had biopsy or VP shunt. However, histological confirmation of germ cell tumors were available in only 42 cases (60.87%). The rest had CT or MRI imaging as pineal region tumors. The most recent World Health Organization classification of germ cell tumors is

germinoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, teratoma and mixed germ cell tumors (13). Germinoma is the predominate subtype followed by mixed germ cell tumors. There was only one case whose histology was benign or mature teratoma. These might not represent the true incidence of histopathology because about 40 per cent did not have tissue biopsy and some benign cases were not sent for further treatment. Moreover, histology depends on the size of tumor sampling, especially when a biopsy was undertaken.

Tumor markers have been used adjunctively to diagnose the histology of the tumors, especially at high elevation. Alpha fetoprotein (AFP) and β-human chorionic gonadotropin (β-HCG) are commonly used. Normal level of these markers are usually noted in pure germinoma. AFP rises in endodermal sinus tumors whereas high serum levels of β-HCG suggest choriocarcinoma(14). Low levels of β-HCG are non-specific. Mild elevation of β-HCG has been noted in some forms of germinoma, choriocarcinoma and other nongerminomatous germ cell tumors. Study of the cerebrospinal fluid (CSF) and serum markers have been reported by Allen JC, et al. They found that the marker profiles correlated with histological diagnosis. CSF marker level is more sensitive than serum markers. These biological markers can be used as an indicator for treatment success and follow-up(15). Because of the inconsistency of the retrospective data, correlation of the markers and histology could not be assessed in the present study.

The definite role of surgical tumor removal, radiotherapy and chemotherapy in intracranial germ cell tumors remains unsettled. Historically, due to the morbidity of the surgical approach in these locations, radiation treatment was used as a test of histology. After 2,000 cGy was delivered to the tumor, the patient was reevaluated. If good response was obtained, a diagnosis of germinoma was assumed and craniospinal irradiation (CSI) continued(16). Nowadays, this policy is no longer appropriate. All patients should have histological confirmation before treatment.

A pineal tumor is one of the most difficult brain tumors to remove. In the present study, tumor removal was obtained in approximately 30 per cent. The current recommendation is to obtain a tissue diagnosis and when possible, to carry out a gross total tumor removal(1). Resection is necessary in a benign lesion such as a mature teratoma which is relatively radioresistant. There was one patient with a mature cystic teratoma, and total tumor removal without postoperative radiation treatment was done. At his last visit which was 4 years after treatment completion, he remained disease free.

Radiation therapy has an established role in intracranial germ cell tumors. In the present analysis, overall survival rates at 3 and 5 years were 86.45 per cent and 81.64 per cent, respectively. Because of the small number of patients, survival analysis by each histology was not assessed. Five year survival rates with radiation therapy ranging from 30-90 per cent were reported depending on histology and extent of disease, age and radiation dose and volume(1-4,7, 8). Wolden et al reported 91 per cent 5-year disease free survival rate for germinoma, 63 per cent for unbiopsied tumors and 60 per cent for non-germinomatous germ cell tumors with a radiation treatment dose of 50-54 Gy to the primary tumor with or without whole brain or whole ventricular irradiation(17).

The incidence of CSF seeding in germinoma ranged from 7-12 per cent. Entire ventricular system or even entire craniospinal axis irradiation had been recommended in the past. In some reports, an inferior survival rate was achieved in patients who had smaller irradiated volume than whole brain irradiation(1,18). In current articles with complete diagnostic craniospinal evaluation, prophylactic spinal irradiation was not justified because the risk of spinal metastasis for germinoma was minimal. Spinal irradiation is recommended in patients with malignant CSF cytology or known leptomeningeal metastases(17,19). With RT alone, the standard radiation dose is 24-36 Gy to the whole ventricular system or CSI followed by boost to the primary tumor to 50-54 Gy. Because of the deleterious effects of radition treatment especially on the immature nervous system, neoadjuvant chemotherapy has been attempted to either reduce or eliminate radiation therapy.

Allen JC, et al reported a phase II trial of preirradiation chemotherapy in CNS germinoma. Their patients who had complete response to neoadjuvant chemotherapy received a reduced dose radiation, 30 Gy for an involved field and 21 Gy for CSI. Localized disease was treated with an involved field, whereas craniospinal irradiation was for disseminated disease. Ten of their 11 patients were in remission for a median of 25 months(20). There was a report of chemotherapy without radiation in intracranial germ cell tumors from The First International Central Nervous System Germ Cell Tumor Study. They concluded that about

50 per cent of newly diagnosed intracranial germ cell tumors could be successfully treated with chemotherapy alone[21]. However, this approch is still under investigation.

The management of nongerminomatous germ cell tumors (NGGCT) is still controversial. Prognosis of NGGCT is poorer than germinoma with a higher incidence of spinal metastases. Systemic chemotherapy is an important part of treatment in NGGCT. Platinum-based chemotherapy has been extensively studied including high-dose chemotherapy and autologous stem-cell rescue[22-27]. These reports demonstrated that systemic chemotherapy appears to be efficacious in the treatment of intracranial nongerminomatous germ cell tumors. However, if chemotherapy is not feasible, craniospinal irradiation is justified to control spinal disease[28,9]. As in the present report, only one of 16 patients who received prophylatic spinal radiation had spinal relapse during follow-up. Moreover, 7 of 8 cases who had spinal relapse did not obtain prophylactic spinal radiation.

SUMMARY

Radiation therapy has been an effective treatment, which was able to control the majority of patients with intracranial germ cell tumors. However, because radiation therapy has deleterious side effects especially in children and the disease usually occurs in young adults and children, the future trend is likely to be more aggressive chemotherapy to reduce the dose and volume of radiation therapy.

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มะเร็งของสมองชนิดเยอร์ม เซลล์ : ประสบการณ์ในโรงพยาบาลจุฬาลงกรณ์

กาญจนา โชติเลอศักดิ์, พบ, ประยุทธ์ โรจน์พรประดิษฐ์, พบ*, เทวินทร์ โชติธนประสิทธิ์, พบ*, ชวลิต เลิศบุษยานุกูล, พบ*, ประเสริฐ เลิศสงวนสินชัย, พบ*, ชลเกียรติ ขอประเสริฐ, พบ*, นพดล อัศวเมธา, พบ*, ศิวลี สุริยาปี, วศม*, โชติกา จำปาเงิน, วทม***

การศึกษาย้อนหลังในผู้ป่วย 69 ราย ที่ได้รับการวินิจฉัยโรคมะเร็งของสมองชนิด Germ cell และได้รับการรักษาที่สาขารังสีรักษา ภาควิชารังสีวิทยา โรงพยาบาลจุฬาลงกรณ์ ระหว่างปี พ.ศ. 2533-2543 อายุเฉลี่ยของผู้ป่วยเท่ากับ 15 ปี ผู้ป่วย 42 ราย (60.87%) มีผลพยาธิวิทยา ยืนยันว่าเป็นเนื้องอกชนิด Germinoma หรือ Nongerminoma พบว่า germinoma เป็นชนิดที่ พบมากที่สุด รองลงมาคือ mixed germ cell tumor ต่อม Pineal และ suprasellar เป็นตำแหน่งที่พบ ได้บ่อยที่สุด 75.36% และ 11.59% ตามลำดับ ผู้ป่วยส่วนใหญ่ (85.5%) มาด้วยความดันในสมองสูง มีผู้ป่วยเพียง 13 ราย ที่มีผลการตรวจเซลล์จากน้ำไขสันหลัง หรือผล MRI ของไขสันหลัง มีการ ตรวจหาค่า Alpha fetopretein หรือ β-human chorionic gonadotropin ใน 66.67% ของผู้ป่วย การผ่าตัดสามารถเอาเนื้องอกในสมองออกได้หมดหรือเกือบหมดได้ 24 ราย ปริมาณรังสีเฉลี่ยที่ ให้ทั้งสมองเท่ากับ 3,600 cGy ในขณะที่ก้อนเนื้องอกปฐมภูมิในสมองได้รับปริมาณรังสีเฉลี่ย 5,400 cGy ผู้ป่วย 17 ราย ได้รับการฉายรังสีที่ไขสันหลัง อัตราการปลอดโรคที่ 5 ปี เท่ากับ 73.59% และอัตราการรอดชีวิตที่ 3 ปี และ 5 ปี เท่ากับ 86.45% และ 81.64% ตามลำดับ

คำสำคัญ : มะเร็งสมองชนิดเยอร์มเซลล์

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