Teratomas of the central nervous system: treatment considerations based on 34 cases

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Object. The optimum clinical management of central nervous system (CNS) teratomas, particularly postsurgical adjuvant therapy, is still unclear, partly as a result of the tumors’ low incidence. In this study the authors analyze 34 cases of CNS teratomas so that they may adequately indicate management of these lesions.

Methods. The median age of the 34 patients was 13 years. Twenty-seven patients treated between 1970 and 1991 were retrospectively reviewed. Four of these 27 patients died as a result of radical surgery, each of them had a teratoma involving the hypothalamus. After initial treatment, which included radiation therapy, 20 patients (48%) had died. In all seven cases of mature teratomas there was no recurrence. In two cases of immature teratomas in which there was complete surgical resection there was recurrence; however, salvage therapies were effective. Seven of eight patients with highly malignant teratomas died; for these patients salvage therapies, including repeated radiation and chemotherapy, failed. Seven patients who presented with CNS teratomas between 1992 and 1996 received adjuvant chemotherapy and radiation therapy according to a prospective study protocol. All seven patients were free from recurrence with a 70 to 100% Karnofsky Performance Scale score at a median follow-up period of 41 months. Patients with CNS teratomas rarely responded completely to chemotherapy or radiation therapy; an effective adjuvant therapy produced a partial response at best.

Conclusions. Because teratomas show various responses to adjuvant therapy, a misdiagnosis of their histological subtype will lead to inadequate therapy. A diverse therapeutic protocol based on histological diagnosis is necessary to plan appropriate management. Treatment recommendations are discussed in detail in the article.

Key Words • brain neoplasm • chemotherapy • germ cell tumor • management • radiation therapy • teratoma

Teratomas in the central nervous system (CNS) are uncommon neoplasms that occur primarily in pediatric populations. The incidence of teratomas, including the malignant type, accounts for 0.4% of all primary brain tumors in Japan. In Tapper and Lack’s study of 254 teratomas in patients who were 21 years of age or younger, 102 teratomas arose in the sacrococcygeal area, 94 in the ovary, 14 in the head and neck area, 12 in the retroperitoneum, 11 in the mediastinum, nine in the CNS, eight in the testes, two in the liver, one in the abdominal wall, and one in the back region. Of these, 124 tumors (49%) were detected during the neonatal period. According to this report, CNS teratomas constitute only 3.5% of all pediatric teratomas. Because of their unique pathological and clinical features, CNS teratomas, particularly those in newborns, have been studied in numerous single case reports published in the literature. Teratomas in the CNS are histologically subcategorized as germ cell tumors (GCTs). Outcomes have improved remarkably for patients who have germinoma and issues in the adjuvant therapy of malignant GCTs such as embryonal carcinoma and endodermal sinus tumor have frequently been discussed in the literature. However, nonsurgical management of CNS teratomas has not been given much attention. Traditionally, CNS teratomas have been grossly analyzed in the series of pediatric pineal region tumors or nongerminomatous GCTs, which include both mature teratoma and embryonal carcinoma in a single category. Although several review articles on CNS GCTs have provided a summary of the natural history and clinical behavior of teratomas, appropriate clinical management of CNS teratomas is still not fully worked out, in part because of their low incidence and an incomplete understanding of their sensitivity to adjuvant therapy.

It is well known to neurosurgeons that mature teratomas can be cured by surgery alone, but this may not be true of other types of teratomas. When therapy for teratomas entails surgical removal alone, the recurrence rate for immature or malignant teratomas turns out to be much higher than that for mature teratomas. It has recently been reported that the probability of 10-year survival...
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was greater than 90% for patients with mature teratomas, whereas the rate was approximately 70% for patients with immature teratomas, and there was a less than 50% chance of 5-year survival in patients who had teratomas with a malignant component. In addition, teratomas that had high serum levels of human chorionic gonadotropin (HCG) and/or α-fetoprotein (AFP) may show poorer treatment responses than those with the same histological feature and normal levels of these markers. Furthermore, CNS teratomas contain diverse cell lineages that may retain an embryonal character and display phenotypical differentiation that may be attributed to the three classic germ layers. Teratomas arising in the CNS are occasionally overgrown by cancers of a somatic type, which are widely assumed to derive from the “malignant transformation” of teratomatous tissues. The emergence of this malignant tissue is often associated with fatal treatment failure.

These CNS teratomas appear extremely heterogeneous in their responses to therapy. Therefore, the planning of their management may depend on further histological subclassification of CNS teratomas. Detailed analyses of patient outcomes related to given treatment modes currently seem to be important. In this study we analyze our experience in treating 34 patients with CNS teratomas so that we can adequately indicate their management. Our study population included 27 patients treated between 1970 and 1991 who were retrospectively reviewed, and seven patients treated between 1992 and 1996 according to our prospective study protocol who were evaluated to assess the accuracy of the protocol in a preliminary manner.

Clinical Material and Methods

Between 1970 and 1996, primary CNS teratoma was diagnosed in a total of 38 consecutive patients at the Hokkaido University Hospital. Histological verification of the lesion was not obtained in four patients: three were treated by radiation therapy alone and one was observed and did not receive any therapy. In the present study we analyze the remaining 34 cases of histologically verified CNS teratomas (Table 1). These 34 patients were divided into two groups based on the time period in which they were treated, and the groups were assessed separately. Records of the early group, which consisted of 27 patients with primary CNS teratomas treated between 1970 and 1991, were retrospectively analyzed, whereas seven patients treated between 1992 and 1996 were participants in a prospective clinical trial conducted at Hokkaido University Hospital. Patients with a histological diagnosis of primary CNS teratoma who had not been treated previously were eligible for enrollment. A total of seven consecutive patients were enrolled between 1992 and 1996. These seven patients were uniformly treated based on a histological subclassification of teratomas, and the preliminary results of treatment were analyzed.

Patient Characteristics

The median age of the 34 patients at initiation of treatment was 13 years (range 2–37 years) and the male/female ratio was 26:8. At diagnosis, 16 patients had solitary hypothalamo-hypophyseal disease, 13 had solitary pineal disease, four had multifocal disease in both regions, one had basal ganglia disease, and none had disseminated disease. Fifteen patients (44%) had obstructive hydrocephalus. Fourteen of 15 patients with a pineal mass presented with symptoms and signs of hydrocephalus at diagnosis.

There were eight mature teratomas, one mature teratoma mixed with germinoma, one mature teratoma with malignant transformation, seven immature teratomas, six immature teratomas mixed with germinoma, seven immature teratomas mixed with embryonal carcinoma, one immature teratoma mixed with choriocarcinoma, and three immature teratomas with malignant transformation (Table 1). Of the 24 patients in whom tumor markers were examined before treatment, 17 showed elevated levels of HCG-β and/or AFP in serum and/or cerebrospinal fluid; 12 patients had elevated levels of HCG-β and 13 patients had elevated levels of AFP. Two of six patients with pure mature teratoma showed slightly elevated levels of HCG-β or AFP, respectively.

Treatment Outline From 1970 to 1991

The treatment plan for this condition changed over the 20 years preceding 1992. Empirical radiation therapy (median tumor dose 15 Gy; range 12–25 Gy) before surgical removal was used throughout the 1970s in seven patients who were thought to have germinomas, because germinomas were known to have a conspicuous radiation sensitivity, and the incidence of surgical morbidity in patients with this type of lesion was high. Tumors that were resistant to empirical irradiation were subjected to surgical removal (Table 1).

Table 2 shows the initial adjuvant therapy given to 23 patients treated between 1970 and 1991; data obtained in four patients who died as a result of their first radical surgery were excluded from this table. Radiation therapy, except that given empirically, was given to 15 of the 23 patients. Of the remaining eight patients who did not receive radiotherapy, three patients had mature teratomas, two had immature teratomas that were totally resected, one patient had an immature teratoma mixed with germi-
TABLE 2

Initial therapy and final outcome in 23 patients treated between 1970 and 1991*

<table>
<thead>
<tr>
<th>Histological Diagnosis</th>
<th>No. of Patients</th>
<th>RT (Gy)</th>
<th>Chemo</th>
<th>Remission</th>
<th>Recurrence (TTP in mos)</th>
<th>Survival Rate (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MT</td>
<td>7</td>
<td>4 (35, 40, 45, 53)</td>
<td>0</td>
<td>7</td>
<td>1 (56)</td>
<td>7 (100%) (26, 58, 124, 158, 173, 277)</td>
</tr>
<tr>
<td>IT</td>
<td>3</td>
<td>1 (55)</td>
<td>0</td>
<td>3</td>
<td>2 (3, 53)</td>
<td>3 (100%) (78, 138, 217)</td>
</tr>
<tr>
<td>IT w/ germinoma</td>
<td>5</td>
<td>4 (40, 51, 55, 60)</td>
<td>2</td>
<td>4</td>
<td>3 (4, 4)</td>
<td>2 (3, 4)</td>
</tr>
<tr>
<td>IT w/ embryonal ca</td>
<td>5</td>
<td>5 (45, 45, 48, 50, 56)</td>
<td>1</td>
<td>3</td>
<td>3 of 4 (0, 4.7, 26)</td>
<td>3 (40%) (4, 33, 65, 79, 180)</td>
</tr>
<tr>
<td>IT w/ choriocarcinoma</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>0 (0%) (1†)</td>
</tr>
<tr>
<td>IT w/ malignant trans</td>
<td>2</td>
<td>1 (45)</td>
<td>0</td>
<td>2</td>
<td>2 (5, 117)</td>
<td>0 (0%) (7†, 174†)</td>
</tr>
</tbody>
</table>

* Four patients who died of the first surgery were excluded. Abbreviations: ca = carcinoma; chemo = chemotherapy; malig trans = malignant transformation; RT = radiation therapy; TTP = time to progression; — = not applicable.
† Patient died.

As a salvage therapy various chemotherapies were used in six patients with recurrent disease. The agents used were cisplatin, carboplatin, etoposide, ifosfamide, methotrexate, and vinblastine.

The extent of surgical resection that had been performed was determined from surgical records, postoperative computerized tomography (CT) scans, and magnetic resonance (MR) images, although in six patients who were surgically treated before the CT era only the surgical record was used for assessment. Because an immature teratoma and its mixed components often invade adjacent neural tissue, gross-total resection represented a complete removal of visible tumor; subtotal resection, 95% or more volume reduction; partial resection, 5 to 95% volume reduction; and a biopsy sample, less than 5% resection. Recurrent disease was defined as the radiographic appearance of new tumor(s), the elevation of tumor markers, or neurological worsening with later evidence of tumor growth in patients who had previously experienced a complete remission of disease.

TABLE 3

Postsurgical therapeutic regimens for CNS teratomas since 1992*

<table>
<thead>
<tr>
<th>Type of Teratoma</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>MT</td>
<td>EP regimen 3 cycles (no irradiation)</td>
</tr>
<tr>
<td>MT mixed w/ germinoma</td>
<td>3–6 cycles of ICE regimen: postchemotherapy radiation therapy to a localized field (total dose of 24 Gy in 12 fractions over 3 wks after complete resection; total dose of 44 Gy in 22 fractions over 5 wks for residual tumor); (craniospinal irradiation of 24 Gy in 12 fractions over 3 wks only for dissemination)</td>
</tr>
<tr>
<td>IT mixed w/ or w/out germinoma</td>
<td>4–6 cycles of ICE regimen: concurrent radiation therapy to craniospinal field (total dose of 4 Gy in 12 fractions over 3 wks) w/ a local boost (total dose of 30 Gy in 15 fractions over 4 wks)</td>
</tr>
</tbody>
</table>

* EP regimen = etoposide 100 mg/m²/day and cisplatin 20 mg/m²/day; 2 hours each for 5 consecutive days; ICE regimen = ifosfamide 900 mg/m²/day, cisplatin 20 mg/m²/day, and etoposide 60 mg/m²/day, 2 hours each for 5 consecutive days.

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gm/m²/day), and etoposide (60 mg/m²/day), which were administered as described in detail elsewhere.

Patients who had mature teratomas received three cycles of the EP regimen alone without radiation therapy. Patients with mature or immature teratoma mixed with or without germinoma first received the ICE regimen. Three cycles were given in cases in which gross-total surgical resection was achieved with normalized levels of serum HCG-β and AFP. If there was a nearly complete disappearance of measurable mass on MR images (> 95% decrease in volume) and if normalized levels of tumor markers were detected after one or more cycles of chemotherapy, then three more cycles of ICE therapy were added, up to a maximum total of six cycles. Subsequently, radiation to the involved field was administered at a dose of 24 Gy (12 fractions over 3 weeks) to patients in whom complete remission was achieved, and at a dose of 44 Gy (22 fractions over 5 weeks) to patients who had a residual mass after chemotherapy.

Patients who had either a teratoma with malignant transformation or a mature or immature teratoma mixed with embryonal carcinoma, a yolk sac tumor, or a choriocarcinoma underwent the ICE regimen with concurrent radiation therapy. Four cycles were given in cases in which gross-total surgical resection was achieved with normalized levels of serum HCG-β and AFP. If there was a nearly complete disappearance of measurable mass on MR images (> 95% decrease in volume) and normalized levels of the tumor marker were detected after one or more cycles of chemotherapy, then three more cycles of ICE therapy were added, up to a maximum total of six cycles. Concurrently, patients were given 24-Gy (12 fractions over 3 weeks) craniospinal radiotherapy with a local boost of 30 Gy (15 fractions over 4 weeks).

An evaluation of the extent of disease was made using whole-neuraxis MR imaging (T₁-weighted contrast-enhanced imaging) and a marker study, which were performed after every cycle of chemotherapy and radiation therapy. During the follow-up period, MR imaging and the marker study were repeated every 4 to 6 months. The percentage of tumor decrease was determined by measuring tumor volume on MR imaging. A partial response was defined as a greater than 50% decrease in tumor volume and additional normalization of serum HCG-β and AFP levels; progressive disease was defined as an increase in either tumor volume or the level of tumor markers. Stabilized disease involved a tumor whose volume was stable or decreasing for more than 12 months. The treatment plan recommended second-look surgery in patients whose tumor was evaluated as progressive or stable disease during or after all scheduled chemoradiation therapy. Progression-free survival was defined as the interval from surgery to relapse, progression, or last follow-up evaluation. The median follow-up time was 41 months (range 14–55 months).

Results

Surgical Removal of Tumor and Incidence of Patient Mortality

Table 1 provides a summary of the histological diagnoses and extents of surgery in all patients. These histological subtypes of teratomas were indistinguishable by evaluating preoperative clinical manifestations and neuroimaging studies. Between 1970 and 1991, a total resection was achieved in 15 patients, including eight patients with solitary pineal lesions and seven patients with hypothalamohypophyseal lesions. A subtotal or partial resection was performed in nine patients, and a stereotactic biopsy specimen was obtained in three patients. There were four deaths directly related to radical surgery and thus the operative mortality rate in this early period was 15% (four of 27 patients).

The four patients who died as a result of surgery had teratomas involving the hypothalamus; two of these patients presented preoperatively with severe hypothalamic dysfunctions such as hypernatremia and consciousness disturbance. A 16-year-old patient with an immature teratoma that originated in the hypothalamus and extended into the third ventricle first received 25 Gy of empirical radiation therapy. Because of the progressive growth of the tumor during radiation therapy, the tumor was totally resected by means of the transcallosal route. This patient died of hypothalamic dysfunction 2 weeks after surgery. An 11-year-old patient with a large suprasellar immature teratoma underwent total removal of the tumor via a subfrontal route and died of hypothalamic dysfunction 4 days after surgery. A 13-year-old patient with a suprasellar immature teratoma that originated in the hypothalamus and extended into the third ventricle first received 17.5 Gy of empirical radiation therapy. This therapy failed and a total removal was performed via an interhemispheric approach. The patient became comatose after the surgery and died 6 months later without relapse of the tumor. A 22-year-old patient with a suprasellar immature teratoma with malignant transformation (squamous cell carcinoma) that originated in the hypothalamus and extended into the third ventricle first received 12 Gy of empirical radiation therapy, but the tumor grew rapidly during the radiation therapy. The tumor was subtotally resected via the transcallosal route. This patient died of hypothalamic dysfunction 6 weeks after the surgery.

Seven patients were surgically treated between 1992 and 1996. Radical removal of tumor was performed only for four pineal teratomas, whereas biopsy specimens were obtained in three hypothalamohypophyseal teratomas (Table 1). All four pineal teratomas were completely resected. There was no incidence of mortality or morbidity related to surgery in this later period.

Outcomes for Patients Treated Between 1970 and 1991

When analyses of 27 patients treated before 1991 were performed in January 1998, 14 of the patients were alive and 13 were deceased. Table 2 shows the remission, recurrence, and survival rates for this entire group, with a median follow-up period of 65 months. Twenty patients (74%) achieved remission at least 3 months after initial surgery or radiotherapy, whereas seven patients did not. The levels of tumor markers had no impact on the patient’s outcome, although these were useful for monitoring disease status.

None of the seven mature teratomas recurred after initial treatment. Three of these patients underwent total removal of tumor with no adjuvant therapy, one patient...
underwent total removal and radiation therapy, two patients underwent partial removal and radiation therapy, and one patient underwent biopsy alone. All of these patients were alive and without tumor progression at the final observation.

Of the six patients with immature teratomas, three died as a result of surgery and tumor remission was achieved in three. One surviving patient underwent partial removal and received 40-Gy whole-ventricle field radiation therapy with a 15-Gy local tumor boost. The other two surviving patients underwent total surgical resection without adjuvant therapy, and they experienced tumor recurrence at 3 and 53 months after surgery, respectively. As a salvage therapy, one patient underwent whole-brain radiation treatment and another patient received radiation therapy that included craniospinal field and chemotherapy composed of etoposide and carboplatin. These salvage therapies were effective in both patients. These two patients were in their second remission at the final observation.

Two of five patients who had immature teratomas with a component of germinoma died. One patient was given chemotherapy composed of cisplatin and etoposide after a biopsy procedure and was then treated with 40 Gy of localized radiation therapy. This patient died of tumor dissemination soon after completing the adjuvant therapy. Another patient underwent 55-Gy whole-brain radiation therapy; however, 4 months later spinal dissemination occurred. Salvage radiation therapy with a dose to the craniospinal field was effective, but this patient died of a second recurrence 24 months after the salvage therapy. In these two patients, cerebrospinal tumor seeding was thought to have been missed during an insufficient radiological examination at the initial diagnosis. Of the three survivors with this condition, one patient underwent total tumor removal alone. A local recurrence occurred, but successful salvage was accomplished by administering chemotherapy consisting of cisplatin, etoposide, and vinblastine, in combination with 50-Gy local radiation therapy. The other two patients were given localized radiation therapy after a total resection and a subtotal resection, respectively, and have been free of tumor since this treatment.

Eight patients had teratomas that included a highly malignant component, such as embryonal carcinoma, choriocarcinoma, or other cancers. Seven of these patients died. The one patient who was alive 150 months after initiation of therapy had undergone with partial tumor removal and radiation therapy to the whole-brain field (36 Gy) with a local tumor boost (20 Gy). Of the seven deceased patients, one died as a result of radical surgery. One patient with immature teratoma mixed with choriocarcinoma underwent partial tumor removal, but adjuvant therapy could not be given because of aggressive tumor progression postsurgery. Remission was achieved in five patients for respective durations of 4, 5, 7, 26, and 117 months. Of these five, one patient underwent total surgical removal without additional therapy, two patients received radiation therapy, and two patients received radiation therapy combined with chemotherapy consisting of cisplatin and etoposide. Salvage therapy including repeated radiotherapy and combination chemotherapy was not effective in these patients, except in one patient whose recurrence was histologically categorized as pure germinoma.

Outcomes for Patients Treated Between 1992 and 1996

Table 4 shows the results of treatment and outcomes in the seven patients with newly diagnosed teratomas treated from 1992 to 1996. All patients were free from recurrence at a median follow-up period of 41 months (range 23–55 months). Six patients had elevated levels of HCG-β and/or AFP at diagnosis. These tumor markers were negative in all patients during the follow-up period. At the final observation, each patient’s Karnofsky Performance Scale status was 70% or higher.

Four patients with a solitary pineal teratoma first underwent total surgical resection and then received adjuvant therapy as shown in Table 4. These patients were free of disease at the final observation. The remaining three patients in whom teratoma was diagnosed at biopsy had postsurgical disease that could be evaluated on MR imaging. One patient with a hypothalamic immature teratoma received ICE chemotherapy and radiation therapy. The response to the chemotherapy was evaluated as a partial response, and 44 Gy of local radiation further reduced the volume of tumor. The tumor has been stable in size for 41 months. One patient with a suprasellar mature teratoma mixed with a minor component of germinoma underwent a transsphenoidal biopsy procedure and received ICE chemotherapy, but the tumor grew during the chemotherapy. A second radical surgery successfully controlled the tumor in this patient (Fig. 1). One patient with a multifocal immature teratoma mixed with embryonal carcinoma was also given six cycles of ICE chemotherapy and 24-Gy craniospinal radiation therapy with a 30-Gy local tumor boost. This patient achieved a partial response and the disease was stabilized (Fig. 2).

A total of 30 cycles of chemotherapy were performed in seven patients (Table 4). Both the EP and ICE regimens were well tolerated by all patients. There was no significant hematoma, hepatotoxicity, or nephrotoxicity. The cisplatin ototoxicity was not profound; only mild high-tone hearing loss (> 40 dB in the 4000–8000 Hz range) was recorded in one patient. The most significant toxic effect in both regimens was hematological in nature. Because of myelosuppression induced by the chemotherapy with or without concurrent radiation therapy, granulocyte–colony stimulating factor was needed in all patients, and dose reduction of chemotherapeutic agents following protocol criteria was required in 11 of 30 cycles.

Illustrative Cases

Among the 34 cases, there were 10 recurrences (or relapses) after tumor remission following the initial therapy (Table 2). The pattern of the recurrence was noteworthy.

In 1990, two patients with neurohypophyseal teratoma underwent complete surgical resection via the transsphenoidal route, and their tumors were histologically diagnosed as mature teratomas. Adjuvant therapy was not given to these patients, but 3 months after surgery, both tumors recurred. A thorough histological reexamination of specimens obtained at these patients’ first surgeries revealed, in one case, a very small immature component and, in the other, a tiny portion of immature teratoma.
including germinoma. These two patients survived for 78 and 79 months, respectively, after salvage chemoradiation therapy. Two other pineal teratomas, which were initially diagnosed as immature teratomas with a tiny component of embryonal carcinoma, recurred as pure embryonal carcinomas. In another patient, an immature teratoma including undifferentiated carcinoma and germinoma recurred as a pure germinoma 117 months after the initial therapy, as revealed by autopsy. Another patient suffered a metachronous germinoma in the neurohypophyseal region 8 years after complete removal of a pineal mature teratoma; this was not considered to be a recurrence and has been reported elsewhere.  

A complete response to chemotherapy and/or radiation therapy is rarely achieved in patients with CNS teratomas; effective adjuvant therapy usually produces a partial response at best. In this series, a complete response was achieved in only one patient after receiving 45 Gy of radiation therapy. The tumor in this patient recurred and was a lethal embryonal carcinoma. Figure 2 shows a represen-

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Histological Diagnosis</th>
<th>Extent of Surgery</th>
<th>Surgery Regimen</th>
<th>Radiotherapy Field (Gy)</th>
<th>Progression-Free Survival (mos)</th>
<th>Final Outcome</th>
<th>Karnofsky Performance Status (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MT</td>
<td>total</td>
<td>EP</td>
<td>3</td>
<td>none</td>
<td>NE</td>
<td>49+</td>
</tr>
<tr>
<td>2</td>
<td>IT</td>
<td>biopsy</td>
<td>ICE</td>
<td>6</td>
<td>LP (44)</td>
<td>PR</td>
<td>41+</td>
</tr>
<tr>
<td>3</td>
<td>MT w/ germinoma</td>
<td>biopsy</td>
<td>ICE</td>
<td>3</td>
<td>none</td>
<td>PD</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>IT w/ germinoma</td>
<td>gross total</td>
<td>ICE</td>
<td>3</td>
<td>LP (24)</td>
<td>NE</td>
<td>23+</td>
</tr>
<tr>
<td>5</td>
<td>IT w/ embryonal ca</td>
<td>gross total</td>
<td>ICE</td>
<td>6</td>
<td>LP (30) CS (24)</td>
<td>NE</td>
<td>55+</td>
</tr>
<tr>
<td>6</td>
<td>IT w/ embryonal ca</td>
<td>biopsy</td>
<td>ICE</td>
<td>6</td>
<td>LP (30) CS (24)</td>
<td>PR</td>
<td>41+</td>
</tr>
<tr>
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<td>gross total</td>
<td>ICE</td>
<td>4</td>
<td>LP (30) CS (24)</td>
<td>NE</td>
<td>34+</td>
</tr>
</tbody>
</table>

* CS = craniospinal; DF = disease free; LP = local primary; NE = could not be evaluated; PD = progressive disease; PR = partial response; SD = stabilized disease.  
† Disease free for 14 months after the second surgical removal.
In such a case, second-tier policy that if total removal of a mature teratoma has been performed, it is not necessary, in principle, to administer adjuvant therapy. It may be current general policy that if total removal of a mature teratoma has been performed, it is not necessary, in principle, to administer adjuvant therapy. In our present protocol (Table 3), however, we use an EP regimen even after total resection of a mature teratoma, because of our previous experience in which histological misdiagnoses occurred in two children with immature teratomas. In these two patients, the initial diagnosis was mature teratoma, but a thorough histological reexamination at the time of recurrence found a tiny amount of immature and germinomatous components in the specimens obtained during the initial surgery. At that time we were concerned about the difficulty of diagnosing the histological malignancy of teratomas. However, in this series none of the eight mature teratomas recurred. It can be concluded that mature teratomas that are completely resected do not require adjuvant therapy; however, because a misdiagnosis in determining the histological subtypes of teratoma leads to inadequate therapy, emphasis must be placed on executing an extremely careful histological analysis in which the entire specimen is examined.

Treatment of certain mature teratomas in the hypothalamic and/or hypophyseal regions is better when partial removal or biopsy is used to preserve hypothalamo-pituitary functions. It has been a matter of controversy whether patients with partially removed mature teratomas should be treated with adjuvant therapy or simply observed until the tumors regrow. Any residual portion of a tumor diagnosed as a mature teratoma may contain a small portion of immature or other malignant tissue, and relapses after a partial removal of mature teratoma have been reported. Adjuvant therapy, therefore, may be necessary after partial removal of a mature teratoma. Although in the literature there is little emphasis on the use of chemotherapy in the treatment of mature teratomas, we have found that cisplatin-based chemotherapy can be effective in targeting suspicious immature components. It is possible, however, that a true mature teratoma might be resistant to the chemoradiation therapy and could eventually grow during adjuvant therapy. In such a case, second-look surgery is the usual method of treating a growing tumor that is resistant to adjuvant therapy. However, because mature teratomas have no invasive properties, it may be feasible to administer dose-intensified stereotactic radiation after a partial resection of a mature teratoma, although at the present time no clinical data on this treatment are available in the literature.

Because patients, particularly children, should not be exposed to the potential toxicities of unnecessary chemotherapy, the indication for chemotherapy in cases of partially resected mature teratomas has to be discussed further, based on the results of a large study in which the
incidence and pattern of recurrence of partially resected mature teratomas are considered.

**Immature Teratomas**

Several authors have already reported that the recurrence rate of immature teratomas is higher than that of mature teratomas. 

Although in some cases spontaneous maturation may be a significant aspect of the natural history of immature teratomas and a spontaneous growth arrest might occur, 

even after total resection immature teratomas require adjuvant therapy.

There has been little information available concerning the response of immature teratomas to adjuvant therapy. Schild, et al., 

reported that delivery of greater than 50 Gy or administration of chemotherapy to mature and immature teratomas was not associated with improved survival in patients. Matsutani, et al., 

performed a retrospective study on 153 patients with intracranial GCTs. The patients with “moderately” malignant tumors, including mixed germinoma plus teratoma or teratoma with a small amount of malignant components, tended to have a lower recurrence rate (11.1%; one of nine patients) if they had received chemotherapy in addition to radiation therapy rather than radiation therapy alone (41.2%; seven of 17 patients).

Although this study included various histological subtypes of CNS teratomas, the results suggest that chemotherapy in combination with radiation therapy had some effectiveness in treating immature teratomas.

Garré and coworkers 

reported on a child who had an immature teratoma with no other type of malignant GCT. Considering the absence of residual tumor after radical surgical removal, they adopted a policy of “wait and see.” One month later, however, the child presented with a rapidly growing mass. Chemotherapy composed of carboplatin, etoposide, bleomycin, ifosfamide, vincristine, and dactinomycin achieved complete remission, and the patient continued free of disease for 24 months. This case addressed the issue of whether chemotherapy alone could be adequate to treat an immature teratoma and showed a positive result.

Baranzelli, et al., 

summarized their experience in treating “secretary” GCTs. Eighteen patients with CNS GCTs, including teratomas, were treated with the TC90 protocol consisting of bleomycin, carboplatin, ifosfamide, and etoposide. If any residual tumor remained after chemotherapy, surgery was to be performed, followed by focal radiation therapy. If there was a complete radiographic response, radiation therapy would be withheld. After three cycles of chemotherapy, all patients showed normalization of tumor markers. Three patients showed tumor growth on MR imaging examinations, and these individuals underwent surgical resection. The pathological investigation performed in the three patients revealed a mature teratoma in one and a mature plus immature teratoma in two. Despite complete normalization of markers after chemotherapy in all 18 patients, 12 of the 13 patients who did not undergo radiation therapy suffered relapse. The recurrence rate has been high after successful chemotherapy as the sole treatment. 

A moderate dose (40–55 Gy) of local radiation to the primary site should also be given in cases of immature teratomas, although conventional radiation therapy carries significant risks of neurological and endocrinological sequelae in young patients.

Combination chemotherapy regimens including cisplatin or carboplatin, etoposide, and ifosfamide have proved effective for refractory gonadal GCTs including teratomas. Since 1992, therefore, we have used the ICE regimen, consisting of ifosfamide, etoposide, and cisplatin, for immature teratomas as well as for teratomas with a malignant component. In our recent series, a total of six patients were treated with the ICE regimen and five of them received radiation therapy. Five of the six patients remained free of disease progression after a median follow-up period of 41 months.

Immature teratomas, as well as mature teratomas, contain extremely diverse cell lineages, and a rigorous histological examination of immature teratomas often reveals a tiny component of germinoma. Immature teratomas show widely varying responses to adjuvant therapy; for example, striking differences in event-free survival after similar therapy regimens have been previously reported.

A teratoma may recur as a different histological subtype, such as germinoma, dermoid cyst, yolk sac tumor, or embryonal carcinoma. Furthermore, immature teratomas may show a paradoxical response to adjuvant therapy, as in some cases in which the chemosensitive component of a given tumor is reduced in size, whereas the other components such as differentiated or chemoresistant tissue simultaneously increase in size. In the present series, as shown in Fig. 1, a suprasellar mature teratoma with a component of germinoma grew as a pure dermoid cyst during chemotherapy. This mixed GCT was evaluated as a chemoresistant tumor, although a portion of the enhancing lesion of this tumor appeared on MR imaging to be reduced in size after the chemotherapy. The second-look radical surgery is an option to treat such cases not only for tumor debulking but also for reexamination of tumor type. Similarly, O’Callaghan, et al., 

recently reported a case of “the growing teratoma syndrome.” A 19-year-old man with a pineal nongerminomatous GCT was treated with chemotherapy. Despite normalization of raised tumor marker levels, the pineal mass enlarged during chemotherapy. This wasexcised and proved to be a mature teratoma.

A review of the literature regarding this complication of intracranial GCTs found that two previously reported cases occurred in children.

**Teratomas With a Highly Malignant Component**

Teratomas occasionally include a component of highly malignant histological characteristics, such as embryonal carcinoma, yolk sac tumor, squamous cell carcinoma, adenocarcinoma, or sarcoma. These malignant neoplasms are often chemoresistant and lethal. Seven of eight patients in the early portion of the present series died of disease progression or recurrence. Packer, et al., 

also treated six patients with embryonal carcinomas by using radiation therapy, either alone or in combination with adjuvant chemotherapy. All patients initially responded to the therapy, but only one has survived for longer than 1 year. Because there is no established effective therapeutic regimen at the present time, the selection of therapeutic modes should be directed toward improving the primary response rate, and the late effects of therapy can be at least partially set aside.

In addition, because targeting all of the heterogeneous tissue components is not practical, adju-
vant therapy should focus on the most malignant tissue in a teratoma.

Dearnaley and colleagues\(^6\) have reported on 12 patients with malignant teratomas; the patients were treated with whole neuraxis radiotherapy, in which 50 Gy was administered to the local tumor and 30 Gy to the remaining brain and spinal cord. The overall and cause-specific actuarial 5-year survival rate was 18.2%, and recurrence was confined to the primary site in six of nine patients. In each case, the tumor recurred rapidly following an initial partial response. The effects of radiotherapy alone in that study and in others have been discouraging.\(^{16,25–27,45–49}\) Matsutani, et al.,\(^3\) treated 11 patients who had immature teratomas or mature teratomas with malignant elements. Three patients received 50 Gy of radiation after surgery and six patients received 60 Gy of radiation and chemotherapy. This treatment resulted in a probable 5-year survival rate of 70.7%. Although the definitions of what constitutes malignant teratoma differ in these two reports, a high-dose radiation therapy in combination with chemotherapy seemed to be useful to treat these malignant neoplasms. In our recent series, three immature teratomas mixed with embryonal carcinoma or adenocarcinoma were successfully treated with ICE chemotherapy and concurrent 54-Gy radiation therapy that included a craniospinal port.

Central nervous system GCTs produce tumor markers that are indicative of malignancy.\(^5\) After treatment with chemotherapy, a residual mass may be found along with normalization of the tumor markers.\(^{5,6,8,20,29,36}\) This phenomenon can be seen as a mass that either persists radiographically or continues to enlarge throughout chemotherapy despite normalization of the markers.\(^5,29\) In such a case, it is possible that the malignant elements of the tumor have been eliminated.\(^5\) Surgical resection of the residue can yield nonmalignant teratoma-like lesions or teratoma mixed with hemorrhagic necrosis and inflammatory cell infiltration, which may be cured with surgical resection alone.\(^5,18\) These occurrences are similar to what is found in systemic GCTs, in which second-look surgery is recommended in the case of marker normalization with chemotherapy. However, findings during surgery usually involve malignant GCT elements.\(^5\) In addition, the results of our study suggest that levels of tumor markers have no impact on patient’s final outcome, although they are useful for monitoring disease status.

Since 1995 with support from the Ministry of Health and Welfare of Japan, a cooperative prospective study to assess a chemotherapy-based treatment protocol has been conducted by the Japanese Pediatric Brain Tumor Study Group. This trial uses a classification for the management of primary CNS teratomas and was designed as a pilot study in which a treatment protocol very similar to ours has been tested. Patients with histologically verified primary CNS teratoma are eligible for this study. To date, a total of 18 cases including five malignant teratomas, eight mixed with GCTs such as immature teratoma with germi-noma, and five with highly malignant GCTs such as embryonal carcinoma have been enrolled. The results of this study will estimate the efficacy of our present treatment protocol.

Conclusions

The management of CNS teratomas is complex because of the heterogeneity of their histological composition. A misdiagnosis of the histological subtype of teratoma will lead to inadequate therapy. Mature teratoma, immature teratoma, and teratoma with a highly malignant component leave patients with good, intermediate, and poor prognoses for survival, respectively. Mature teratomas that are completely resected do not require adjuvant therapy, but the appropriate postsurgical treatment after a partial removal is currently obscure. Immature teratomas are mostly curable or controllable by adding an adequate adjuvant therapy. For highly aggressive teratomas, more extensive resection may be associated with improved patient survival, and postsurgical adjuvant therapy must include multidrug chemotherapy as well as high-dose craniospinal radiotherapy. The results of our new protocol are very preliminary and more prospective studies are needed to gain further insight into this area.

References

Management of CNS teratomas


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