Immature teratomas of the central nervous system: is adjuvant therapy mandatory?

JI HOON PHI, M.D., SEUNG-KI KIM, M.D., PH.D., SUNG-HYE PARK, M.D., PH.D., SEOK HO HONG, M.D., KYU-CHANG WANG, M.D., PH.D., AND BYUNG-KYU CHO, M.D., PH.D.

Departments of Neurosurgery and Pathology, Seoul National University College of Medicine, Clinical Research Institute, Seoul National University Hospital, Seoul, Korea

Object. Immature teratomas of the central nervous system (CNS) are rare neoplasms. Although adjuvant therapy is generally recommended after resection, the exact role of each therapeutic modality is not yet established. The purpose of this study was to analyze the clinicopathological correlation and the role of resection to define the optimal treatment modalities for immature teratomas of the CNS.

Methods. Between 1987 and 2002, eight patients underwent radical surgery for a lesion diagnosed as a CNS immature teratoma at the authors' institution. The clinical courses of these patients and the pathological features of their tumors were retrospectively reviewed.

Gross-total resection (GTR) was achieved in six patients at the initial operation. The mean follow-up period was 75 months. Two patients received postoperative adjuvant therapies and two patients did not, against medical advice. None of the four patients experienced recurrence after long-term follow up. Another four patients, all of whom underwent GTR of the tumor, did not receive adjuvant therapy as part of a prospective treatment scheme. One of them exhibited early recurrence and metastasis. The tumor had pathological features denoting a high-grade (Norris Grade III) lesion and neurocytotomatous differentiation.

Conclusions. Aggressive resection seems to be of utmost importance in the treatment of immature teratomas of the CNS. Adjuvant chemotherapy and radiotherapy can be deferred if GTR is achieved in low-grade, immature teratomas, but adjuvant therapies may be warranted for high-grade ones.

Key Words • immature teratoma • adjuvant therapy • chemotherapy • radiotherapy • central nervous system • pediatric neurosurgery

Teratomas belong to the category of germ cell tumors, and constitute approximately 3% of all pediatric neoplasms. They arise more often in younger populations and represent one half of all so-called “congenital neoplasms.” Most of them arise in the sacrococcygeal region and gonads. Teratomas occurring in the CNS are uncommon, even in Far East Asia, where the incidence of CNS germ cell tumors is much higher than in the Western hemisphere. Although immature teratomas are said to constitute 10 to 50% of teratomas, those arising from the CNS are exceedingly rare. Thus far, anecdotal case reports or limited clinical series have dealt with these uncommon neoplasms.

In general, immature teratomas are notorious for their unpredictable biological behavior and variable clinical course, whether they occur in the CNS or elsewhere in the body. Decades of debate have led to a consensus that extracranial immature teratomas can be effectively treated by complete excision alone and by withholding adjuvant therapies unless recurrence emerges. Subsequently, controversies arose about the natural history and optimal treatment of immature teratomas of the CNS. At present, adjuvant chemotherapy and radiotherapy are generally recommended for such tumors because cases of rapid recurrence after resection have been reported.

We have treated eight cases of immature teratomas of the CNS. For various reasons, some of the patients did not receive adjuvant treatment after resection; however, all of them are still alive without recurrence at long-term follow up. We, therefore, believe that aggressive resection is the best treatment and that adjuvant therapy may be unnecessary for low-grade lesions. For high-grade lesions, adjuvant therapy may still be warranted.

Clinical Material and Methods

Patient Population

Between 1987 and 2002, CNS immature teratomas were identified in eight patients at our institution. Pathological specimens obtained in all cases confirmed that the tumors...
were immature teratomas, with no malignant components of other germ cell tumors.

The cases in which a diagnosis was made by obtaining endoscopic or stereotactic biopsy specimens instead of during the course of a radical resection were excluded because the possibility of a mixed germ cell tumor could not be ruled out. The patients who received primary surgery at other institutions were also excluded.

**Patient Evaluations**

We retrospectively reviewed the patients’ medical records and neuroimaging data. Preoperative MR images were available for seven of eight patients. One patient’s initial MR images had been lost although the interpretation of those images by a neuroradiologist was still available. The degree of resection was evaluated by examining contrast-enhanced CT scans or MR images obtained in the immediate postoperative period or within 6 months of surgery, which were available for all patients. Serum AFP and HCG were checked preoperatively in seven and six patients, respectively.

Preoperative spinal MR images were available for one patient and therefore CSF seeding could be evaluated. Cytological analysis of CSF was undertaken in six patients via either lumbar puncture or external ventricular drainage. Although serum tumor markers and spinal MR images should be checked for all CNS germ cell tumors to establish a proper treatment plan, they were not available for some patients either because the initial diagnosis was that of a mature teratoma or because the patients were critically ill and required an emergency operation, with no time for a complete workup.

During the follow-up period, all patients were evaluated with periodic neurological examinations, MR imaging, and tumor marker studies to ensure early detection of possible recurrence.

**Results**

**Clinical Characteristics**

Eight patients were included in this study: six boys and two girls whose age at surgery ranged from neonate to 11 years (mean 3.9 years). Four patients underwent surgery at or before 2 months of age and two of them met the criteria for so-called “congenital neoplasm.”

The locations of the tumors were pineal (five cases), foramen of Monro (one case), temporal lobe (one case), and spinal cord (one case). A unique case of spinal immature teratoma was an intramedullary tumor in the thoracic region (T4–12). Patients with intracranial tumors presented with headache, vomiting, or an enlarged cranium (which could be attributed to increased intracranial pressure). Those with spinal tumors presented with rapidly progressing paraparesis.

The level of serum AFP was elevated in five patients, with a range of 23 to 5390 ng/ml. Because three patients (Cases 1, 6, and 7) with high serum AFP levels (306, 5390, and 26 ng/ml) were 2 months, 2 weeks, and 2 months of age at the time of diagnosis, respectively, the results can be regarded as normal for their age. Two patients (Cases 2 and 8) were found to have a truly high serum AFP level.

The cytological analysis of CSF demonstrated a lack of malignant cells in all the cases evaluated (six patients), and spinal MR imaging in one patient revealed no metastatic nodule.

**Radical Resection**

Radical resection was attempted for all patients, including one boy (Case 8) who underwent an endoscopic biopsy procedure before radical resection. Gross-total resection was achieved in seven patients. Six patients underwent GTR in a single operation, and one patient (Case 4) whose tumor was initially resected subtotally underwent GTR at the second operation.

**Pathological Considerations**

All immature teratomas were graded according to the system devised by Norris, et al. Four tumors were rated Grade I, one was Grade II, and three were Grade III. The only tumor that recurred after the initial operation (in Case 8) was a Grade III lesion with focal areas of neurocytomatic differentiation.

**Adjuvant Therapies**

Until 1990, local radiotherapy was the primary adjuvant therapy for intracranial immature teratomas at our institution. One patient (Case 2) was treated with postoperative radiotherapy, whereas the parents of another patient (Case 1) refused treatment. From 1990 to 1997, adjuvant therapy consisted of chemotherapy combined with whole neuraxis radiotherapy (36 Gy for whole brain, 18 Gy for local boost, and 24–36 Gy for whole spinal cord). We followed these treatment guidelines for one patient (Case 3) postoperatively. The parents of the other patient (Case 4) treated in this period refused adjuvant therapy for their child.

The patients who underwent GTR after 1998 (Cases 5–8) were followed up cautiously. After weighing the risks and benefits and obtaining informed consent from the parents, prophylactic adjuvant therapies were postponed pending evidence of tumor recurrence.

**Follow Up and Recurrence**

Follow-up periods ranged from 17 to 158 months (mean 75 months). All the patients participated except for one patient (Case 1) who was lost to follow up 102 months after the operation. Tumor recurrence was determined by neurological deterioration not explained by other causes such as shunt malfunction, detection of a mass on MR images, or elevation of serum tumor markers. No evidence of tumor recurrence was found in the patient who was lost to follow up at the time of his last visit.

The four patients who were treated before 1998 survived for more than 6 years without recurrence, regardless of having received adjuvant therapies. The tumor was rated Norris Grade I in three patients and Grade III in the other.

Among the four patients for whom adjuvant therapies were deferred as part of a prospective treatment scheme, three patients (Cases 5–7) were tumor free for 61, 49, and 47 months, respectively, but one patient (Case 8) had early tumor recurrence 6 months after the first operation and underwent a second operation followed by chemotherapy and radiotherapy.

Four patients were left with severe neurological deficits.
Three patients showed developmental delay and mental retardation, and one patient with a spinal tumor, who had flaccid paraplegia before surgery, recovered incompletely and was unable to walk independently. It is significant that all patients with poor functional outcome had tumors when they were younger than 2 months of age. The overall results are summarized in Table 1.

### Illustrative Cases

#### Case 4

This 20-day-old girl was transferred to the emergency department for symptoms of lethargy. There had been no antenatal diagnosis. Her head circumference was 45 cm (95th percentile for her age). Lethargy was prominent, and the fontanels were tense. The “setting sun” sign was observed in both eyes. On brain MR imaging, a huge intraventricular mass of heterogeneous signal intensity was found. Multiple cysts of variable size, intense enhancement of cyst walls, and accompanying hydrocephalus were noted (Fig. 1).

Tumor markers were not checked preoperatively. A cytological analysis of CSF showed a lack of malignant cells. A radical resection was attempted via a transcortical, transventricular route. Thick adhesions near the right foramen of Monro were present, and bleeding from the site hindered complete resection. A ventriculoperitoneal shunt was required to control postoperative progressive hydrocephalus.

Pathological specimens contained mature tissue such as bone and cartilage. Large areas of immature neuroepithelial components supported the diagnosis of immature teratoma, Norris Grade III (Fig. 2). No frank malignancy of either germ line or somatic origin was found. Although chemotherapy and delayed radiotherapy after brain maturation were recommended, the parents of the patient refused adjuvant therapy.

Contrast-enhanced CT scans of the brain obtained 6 months later demonstrated a small residual mass near the right foramen of Monro and marked ventriculomegaly suggestive of shunt malfunction (Fig. 3 left). Endoscopic surgery for complete tumor removal was performed with shunt revision, and a pathological examination revealed a pure mature teratoma.

The patient was followed up for 76 months since the first operation, and recent MR imaging of her brain revealed no evidence of tumor recurrence (Fig. 3 right). Severe developmental delay and mental retardation led to the patient needing full-time, daily care.

#### Case 8

This 5-year-old boy visited the emergency department for severe headache and vomiting that had lasted for days. Bilateral papilledema and limitation of upward gaze were observed. Brain MR imaging revealed a pineal mass 2 cm in diameter and obstructive hydrocephalus (Fig. 4 left). Multiple small cysts and intense enhancement, calcification, and fat components within the tumor aided the neuroimaging diagnosis of teratoma. The level of serum AFP was slightly elevated (23 ng/ml) and that of HCG was within the normal range. After an endoscopic biopsy procedure with third ven-

---

**TABLE 1**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, Sex</th>
<th>Tumor Location</th>
<th>AFP (ng/ml)</th>
<th>Type of Resection</th>
<th>Tumor Grade†</th>
<th>Chemo</th>
<th>RT</th>
<th>Recurrence</th>
<th>FU (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 mos, M</td>
<td>pineal</td>
<td>306</td>
<td>STR</td>
<td>I</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>102</td>
</tr>
<tr>
<td>2</td>
<td>11 yrs, M</td>
<td>pineal</td>
<td>23</td>
<td>GTR</td>
<td>I</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>158</td>
</tr>
<tr>
<td>3</td>
<td>8 yrs, M</td>
<td>pineal</td>
<td>NA</td>
<td>GTR</td>
<td>I</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>neonate, F</td>
<td>foramen of Monro</td>
<td>norm</td>
<td>STR/GTR</td>
<td>III</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>7 yrs, M</td>
<td>pineal</td>
<td>norm</td>
<td>GTR</td>
<td>I</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>61</td>
</tr>
<tr>
<td>6</td>
<td>neonate, M</td>
<td>temporal</td>
<td>5390</td>
<td>GTR</td>
<td>III</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>49</td>
</tr>
<tr>
<td>7</td>
<td>2 mos, F</td>
<td>T4–12</td>
<td>26</td>
<td>GTR</td>
<td>II</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>47</td>
</tr>
<tr>
<td>8</td>
<td>5 yrs, M</td>
<td>pineal</td>
<td>23</td>
<td>GTR</td>
<td>III</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>17</td>
</tr>
</tbody>
</table>

* Chemo = chemotherapy; FU = follow up; NA = not assessed; norm = normal; RT = radiotherapy; STR = subtotal resection.
† Based on Norris, et al. Grade I = immature tissue is present, but the neuroepithelium is absent or limited to only one rare low-power field (× 40) in any slide; Grade II = immature tissue and neuroepithelium are present to a greater degree than Grade I, but the neuroepithelium does not exceed three low-power fields in any slide; Grade III = immature tissue and neuroepithelium are prominent, the latter occupying four or more low-power fields within individual sections.
triculostomy, GTR of the tumor was accomplished via an occipitotranstentorial approach (Fig. 4 right); no neurological deficit occurred. The pathological examination revealed a teratoma with both mature and immature components. Abundant immature neuroepithelial tissue indicated a Norris Grade III. Focal aggregates of oligodendroglia-like cells were found. An immunohistochemical study focusing on neuronal markers, synaptophysin, and neuronal nuclei confirmed neurocytomatous differentiation of the cells (Fig. 5). Spinal MR images obtained 2 weeks postoperatively revealed no CSF seeding, and therefore additional adjuvant therapy was deferred.

Follow-up MR images of the brain obtained 6 months later revealed an enhanced mass in the pineal region, suggesting recurrence (Fig. 6), and spinal MR images also revealed multiple enhancing nodules along the thoracic spinal cord. A second operation was performed, and the tumor was removed subtotally because there was severe adhesion. The patient suffered postoperative hemiparesis of the right side (strength Grade 3). Intensive cisplatin-based chemotherapy and whole-neuraxis radiotherapy (36 Gy for the entire brain, 18 Gy for a local boost, 36 Gy for the whole spinal cord, and 9 Gy as a boost for the spinal enhancing nodule) were given. The child’s motor strength improved sufficiently to allow him to walk independently, but a small residual mass was still visible on MR images of the brain when he was evaluated 11 months postoperatively.

Discussion

Teratomas are tumors composed of tissues derived from three germ cell layers. A diagnosis of immature teratoma can be made if immature tissue of neuroepithelial or stromal origin is found within the tumor. If frank malignant tissue of either germ cell or somatic origin is found, the tumor is classified as either a mixed (malignant) germ cell tumor or a teratoma with malignant transformation.10,11,16 Although this classification appears to be straightforward, confusion in nomenclature has made it difficult to scrutinize the natural history of immature teratomas.10 A thorough pathological examination has been strongly recommended because missing a tiny, immature component within the mature teratoma could result in misdiagnosis.12

Although teratomas are relatively common neoplasms in infancy and early childhood, immature teratomas arising in the CNS are rare. The largest clinical series of CNS teratomas was reported by Sawamura, et al.,16 and included seven cases of pure immature teratoma among 34 total cases of teratoma. Matsutani, et al.,12 reported on an extensive clinical series of 153 cases of CNS germ cell tumors, including seven cases of immature teratoma and four cases of malignant teratoma. These authors analyzed outcomes by
combining immature and malignant teratomas into a single category, which renders it difficult to compare their results with those of other studies. Another clinical study on pineal gland tumors documented the treatment outcome of nine cases of immature teratomas.17

The rarity of immature teratomas of the CNS leads to difficulty in understanding the natural course of the disease and in analyzing treatment outcomes. Other factors also contribute to the uncertainty over treatment. First, the responses of these teratomas to chemotherapy differ significantly among reports. Garre and colleagues7 reported a unique case of complete remission of a recurred CNS immature teratoma after chemotherapy alone, whereas other authors found that immature teratomas had the lowest chemosensitivity among the nongerminomatous germ cell tumors.17,21 These seemingly contradictory results may simply reflect the intrinsic limitations of analyzing small numbers of cases. It is also possible that immature teratomas of the CNS do not represent a uniform disease but a group of diseases within a wide clinicopathological spectrum.

Second, radical resection was not readily achievable before developments in microsurgical techniques and neuroanesthesiological supports. Because the majority of immature teratomas arise in the deep midline area (such as the pineal region), GTR was only possible in one third of the patients.5 Sawamura, et al.,16 reported that three of their seven patients who underwent surgery before 1990 died as a result of surgical complications.

In general, immature teratomas of the CNS have a higher recurrence rate than mature teratomas.7,10,13,15,16 The 10-year survival rate has been reported as greater than 90% for mature teratomas and approximately 70% for immature teratomas.12,15-17 Although the actual roles of surgery and adjuvant therapy for CNS immature teratomas have not been fully established, many clinicians agree on routine postoperative application of intensive chemotherapy and radiotherapy based on reports of these lesions’ rapid recurrence after radical resection.12,15,16

In 1999, a consensus was made in a large intergroup study that extracranial immature teratomas in children could be effectively treated by resection alone.11 The fact that the 3-year event-free survival rate was 93% without adjuvant therapies could represent indirect evidence for withdrawing adjuvant therapy for CNS immature teratomas. Some limitations do exist, however, for extrapolating these results to treatment of CNS immature teratomas. First, the study was a retrospective one, with no control group. Second, there were more recurrences of extragonadal immature teratomas (18%) than gonadal tumors (2%) when treated exclusively by surgery. Finally, in cases of recurrence, the tumors were sufficiently controlled by second surgeries and platinum-based adjuvant chemotherapy. The results of second surgeries and chemotherapy for CNS immature teratomas could differ from those for extracranial tumors because of the higher surgical risks and the effectiveness of chemotherapy being diminished by the blood–brain barrier.

It has been well known that in vivo maturation occurs in ovarian and testicular immature teratomas. This phenomenon of spontaneous maturation has rendered the natural history of CNS immature teratomas additionally unpredictable. In 1996, Shaffrey, et al.,18 first reported unusual cases in which CNS immature teratomas subsequently matured. After reviewing the relevant literature on this issue, these authors emphasized the role of an aggressive surgical approach to these bothersome tumors and recommended judicious use of chemotherapy.

Furthermore, the adverse effects of radiotherapy, especially on the developing nervous system, have been keenly recognized.2,19 Because CNS immature teratomas tend to arise in a very young age group (as in this study), radiotherapy is generally not indicated for fear of its disastrous impact on cognition. Complications of chemotherapy such as neutropenic fever, thrombocytopenia, and secondary malignancy also make it doubtful that this should be considered a routine treatment that is definitely necessary.6

Among four patients treated between 1987 and 1997 at the J. Neurosurg: Pediatrics / Volume 103 / December, 2005
Adjuvant therapy for immature CNS teratomas

our institute, two patients underwent GTR of the tumor and postoperative adjuvant therapies (radiotherapy alone in one patient and radiotherapy plus chemotherapy in the other); both exhibited long-term, disease-free survival. The other two patients also survived for a long time without recurrence, even though their tumors had been managed by resection alone. Furthermore, one of the tumors (Case 4) was rated Norris Grade III, and could have been expected to behave more aggressively. These experiences led to the subsequent treatment plan to postpone adjuvant therapy after total resection until evidence of recurrence.

Since 1998, immature teratomas of the CNS were diagnosed in four patients and GTR was achieved in all cases. One patient with a Norris Grade I pineal tumor (Case 5), another patient with a Grade III temporal lobe tumor (Case 6), and the third with a Grade II spinal intramedullary tumor (Case 7) attained disease-free survival periods of 61, 49, and 47 months, respectively. Another patient (Case 8) who had a Grade III pineal tumor experienced early recurrence and spinal metastasis, with peculiar neurocytomatosus differentiation. Whether these characteristics play some role in the aggressive behavior of the tumor is not known; in one case report of an ovarian mature teratoma from which a central neurocytoma arose, the patient had a good clinical course without recurrence after resection alone.9

Despite considerable criticism, the Norris grading system is generally used to grade immature teratomas. It was first introduced for ovarian immature teratomas and is reported to have a good correlation with recurrence rate and peritoneal seeding.10,13 In sacrococcygeal immature teratomas, however, tumor grading itself is not correlated with the prognosis.10 Whether the grading has prognostic implication in CNS immature teratomas remains to be seen.

There are other indicators for predicting the behavior of CNS immature teratomas. The dissemination of CSF at presentation in itself verifies the aggressiveness of tumor.
Besides those acquired in our patient with a spinal intramedullary tumor, spinal MR images were obtained in only one other patient; the rest underwent cytological examination of CSF. Although the result of these examinations revealed no evidence of dissemination, the lack of complete data made it difficult to evaluate the initial status of tumors.

Serum and CSF tumor markers are other candidates for predictors of biological behavior. Several reports demonstrated that there were poorer outcomes in patients with non-germinomatous germ cell tumors of the CNS with high serum levels of AFP and/or HCG than in those with normal levels of these markers. This result makes sense because tumor markers are secreted from cells that mainly constitute the highly malignant germ cell tumors such as yolk sac tumors and choriocarcinomas; however, the clinical significance of frequent elevations of serum tumor markers in pure CNS immature teratomas has not been clarified. Among the six patients in this study who received no adjuvant therapies, one had not undergone tumor marker examination, four had an age-appropriate serum AFP level, and one (Case 8) had a high serum AFP level. No patient had a high serum HCG level. The fact that the only patient with a high AFP level suffered early recurrence suggests that a high serum AFP level may have prognostic value and that adjuvant therapies should not be deferred in such a case.

If either the Norris Grade or serum AFP level correlates with the prognosis of CNS immature teratomas, one or both could be used to guide a treatment plan, especially adjuvant therapies after an operation. It is premature, however, to draw a definite conclusion with statistical confidence from this study, and it may need to be verified through a randomized trial with more patients.

Conclusions

The natural history of CNS immature teratomas is obscure. Current standards indicate that surgery followed by chemotherapy and radiotherapy is warranted. In our experience, however, some patients survived for a long time with no adjuvant therapies after radical resection. Although surgery seems to have a crucial role in the treatment of CNS immature teratomas, the role of adjuvant therapies requires clarification.

We suggest that the degree of resection, pathological gradings, and serum AFP level can be used to determine in which subgroup of patients with CNS immature teratomas adjuvant therapies can safely be withheld after radical resection. Further study is needed to corroborate this hypothesis and to provide practical guidelines for the treatment of these rare tumors.