Primary intracranial embryonal carcinoma in children: report of two cases with review of the literature

Tao Jiang1,2, Raynald1,2, Hongchao Yang4, Junmei Wang2, Jiang Du2, Wenhui Zhang5, Qiang Shao3*, Chunde Li1*

1Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China; 2Beijing Neurosurgical Institute, Capital Medical University, Beijing, China; 3Department of Neurosurgery, Wuhan Brain Hospital, General Hospital of The Yangtze River Shipping, Wuhan, China; 4Department of Neurointervention Surgery, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China; 5Department of Neurology, The 7th Hospital of Baoding, 071000, Hebei, China. *Equal contributors.

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Abstract: Embryonal carcinoma is a rare malignant brain tumor and stands for 5% of all intracranial germ cell tumors. Embryonal carcinoma occurs mainly in the posterior third ventricle and pineal region area. Preoperative imaging examination, blood serum and cerebrospinal fluid level of AFP and HCG can support the diagnosis. Subtotal to total removal with good preservation of the important structures can be achieved in this tumor resection. Embryonal carcinoma has poor prognosis result. Postoperative radiotherapy and adjuvant chemotherapy may increase the survival rate, but due to the malignant characteristics of the tumor the 5 years survival rate remains low. We presented two cases of embryonal carcinoma in children. Subtotal resection was achieved in these two patients; patient who had had postoperative radiotherapy and adjuvant chemotherapy had longer survival time than patient who had had surgery alone.

Keywords: Embryonal carcinoma, children, germ cell tumor

Introduction

Germ cell tumors are broadly divided into two classes: germinomatous germ cell tumor (GGCT) and non-germinomatous germ cell tumors (NGGCT). Germ cell tumor constitutes less than 0.5% of all intracranial neoplasms; the incidence varies considerably as according to the geographical area. In western countries, they account for only 0.3-3% of primary central nervous system neoplasms, as opposed to 4-12% of incidence in Japan [1]. Primary intracranial embryonal carcinoma is a rare brain tumor. Embryonal carcinoma is part of the NGGCT classification and stands for about 5% of all intracranial germ cell tumors. Eighty percent of this tumor tends to occur along the midline, such as pineal, suprasellar region, hypothalamus and third ventricle [1-3]. Embryonal carcinoma may also occur in different areas other than the midline, such as basal ganglia, parietal lobe and cerebellum [4-6]. Another unusual location of this tumor, which was in the anterior third ventricle, has reported later by Nsir et al [7]. Embryonal carcinoma usually occurs in adolescence and young adult population (10 to 30 years) [1, 8-11].

The symptoms and signs of embryonal carcinoma are varied depending on the location. In sellar area, visual disturbance is commonly present and some may have diabetes insipidus. Among patients who are older than 12 years old, some may manifest in primary or secondary amenorrhea. Whereas for those patients who are younger than 15 years old, growth retardation may occur; these phenomena may resulted by hypothalamic-pituitary failure. Hydrocephalus and midbrain compression syndrome, such as Parinaud’s sign, Argyll Robertson pupil, and diplopia may occur in posterior third ventricle or pineal area embryonal carcinoma. Intracranial hypertension, hemiparesis and epilepsy may occur in the rare case of basal ganglia embryonic carcinoma.
### Table 1. Retrospective study of 15 patients with pure embryonal carcinoma

<table>
<thead>
<tr>
<th>No</th>
<th>Author</th>
<th>Year</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Location</th>
<th>Symptoms</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Suwarindr K</td>
<td>1974</td>
<td>5</td>
<td>Male</td>
<td>Cerebellum</td>
<td>Increasing headache and vomiting</td>
<td>Surgery and radiation</td>
<td>Alive 1 year after operation, no tumor recurrence</td>
</tr>
<tr>
<td>2</td>
<td>Sakata K</td>
<td>1975</td>
<td>8</td>
<td>Male</td>
<td>Pineal</td>
<td>N/A</td>
<td>Total resection, Bleomycin</td>
<td>Died 4 months after operation due to tumor metastasis</td>
</tr>
<tr>
<td>3</td>
<td>Arita N</td>
<td>1978</td>
<td>8</td>
<td>Male</td>
<td>Pineal</td>
<td>N/A</td>
<td>Surgery, radiotherapy, chemotherapy</td>
<td>Died 11 months after operation</td>
</tr>
<tr>
<td>4</td>
<td>Marshal LF</td>
<td>1979</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Surgery, radiotherapy, chemotherapy</td>
<td>Alive 9 months after operation</td>
</tr>
<tr>
<td>5</td>
<td>Nakajima F</td>
<td>1981</td>
<td>14</td>
<td>Male</td>
<td>Anterior third ventricle</td>
<td>Vomiting, disturbance of consciousness</td>
<td>Total resection, chemotherapy (cisplatin, vinblastine, bleomycin)</td>
<td>Alive 12 weeks after operation, no tumor recurrence</td>
</tr>
<tr>
<td>6</td>
<td>Roger J packer</td>
<td>1984</td>
<td>10</td>
<td>Female</td>
<td>Pineal</td>
<td>Headache, weight loss, decreased vision</td>
<td>Biopsy, radiotherapy</td>
<td>Alive 11 months after operation but had local recurrence, later treated with Cyclophosphamide, Adriamycin, Actinomycin but the treatment had no response, died 4 months later due to diffuse dissemination</td>
</tr>
<tr>
<td>7</td>
<td>Maeda Y</td>
<td>1990</td>
<td>17</td>
<td>Male</td>
<td>Basal ganglia</td>
<td>Headache, vomiting, right hemiparesis</td>
<td>Total resection, chemotherapy (cisplatin, vinblastine, bleomycin)</td>
<td>Alive 3 months after operation, no tumor recurrence</td>
</tr>
<tr>
<td>8</td>
<td>Robin F Koeleveld</td>
<td>1991</td>
<td>7</td>
<td>Male</td>
<td>Right parietal</td>
<td>Focal motor seizure involving the left arm</td>
<td>Total resection, chemotherapy (cyclophosphamide, etoposide), radiotherapy</td>
<td>Alive 21 months after operation, no tumor recurrence</td>
</tr>
<tr>
<td>9</td>
<td>Sasaoka Y</td>
<td>1994</td>
<td>15</td>
<td>Male</td>
<td>Basal ganglia</td>
<td>Occasional headache and vomiting, left hemiparesis</td>
<td>Total resection, chemotherapy (etoposide, cisplatin) X 3</td>
<td>Alive 3 months after operation, no tumor recurrence</td>
</tr>
<tr>
<td>10</td>
<td>Wang JN</td>
<td>1995</td>
<td>12</td>
<td>Female</td>
<td>Suprasellar</td>
<td>Secondary amenorrhea, decreased visual acuity, dizziness, postprandial vomiting</td>
<td>Subtotal resection</td>
<td>Died 3 weeks after operation</td>
</tr>
<tr>
<td>11</td>
<td>Ushio Y</td>
<td>1999</td>
<td>8</td>
<td>Female</td>
<td>Suprasellar</td>
<td>N/A</td>
<td>Biopsy, radiotherapy, cisplatin, etoposide, maintenance therapy cisplatin, etoposide (3X)</td>
<td>Alive 118 months after operation</td>
</tr>
<tr>
<td>12</td>
<td>Atef Ben Nair</td>
<td>2014</td>
<td>15</td>
<td>Male</td>
<td>Anterior third ventricle</td>
<td>High intracranial pressure, generalized tonic-clonic seizure</td>
<td>Total resection, chemotherapy (ifosfamide, etoposide, cisplatin)</td>
<td>Alive 2 years after operation, no tumor recurrence</td>
</tr>
<tr>
<td>13</td>
<td>Our case</td>
<td>5</td>
<td>Female</td>
<td>Posterior third ventricle</td>
<td>Paroxysmal headache, nausea and vomiting</td>
<td>Subtotal resection, radiotherapy, chemotherapy (Teniposide, Cisplatin, Ifosfamide)</td>
<td>Alive 6 months after operation, no recurrence of tumor, died 6 months later due to lung metastases</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: N/A = Not available.
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**Table 2. Collective studies from other literatures**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of cases</th>
<th>Outcome</th>
<th>Tumor Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jennings MT</td>
<td>1985</td>
<td>14 cases</td>
<td>2.5 years survival rate (29%)</td>
<td>EC</td>
</tr>
<tr>
<td>Matsutani</td>
<td>1997</td>
<td>11 cases</td>
<td>1 year survival rate (45.5%);</td>
<td>Pure type EC, EST, CC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 years survival rate (27.3%);</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 years survival rate (27.3%)</td>
<td></td>
</tr>
<tr>
<td>Sano K</td>
<td>1999</td>
<td>3 cases</td>
<td>1 year survival rate (80%);</td>
<td>EC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 years survival rate (40%);</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 years survival rate (20%)</td>
<td></td>
</tr>
<tr>
<td>Robertson</td>
<td>1997</td>
<td>18 cases</td>
<td>4 year progression free survival (67%)</td>
<td>NGGCT</td>
</tr>
<tr>
<td>Calaminus G</td>
<td>1997</td>
<td>19 cases</td>
<td>12 months progression free survival (81%)</td>
<td>NGGCT</td>
</tr>
<tr>
<td>Ushio</td>
<td>1997</td>
<td>2 cases</td>
<td>4 year progression free survival (60%)</td>
<td>NGGCT</td>
</tr>
</tbody>
</table>

**Figure 1.** A: The tumor was located at posterior third ventricle and showed isodense on CT scan. B-D: MRI showed slight hypointense on T1-weighted sequences and displayed a strong contrast enhancement.

Alpha-fetoprotein (AFP) and human chorionic gonadotropin (HCG) level may support the diagnosis of embryonal carcinoma. AFP is produced by the yolk sac in the early stage of development and HCG is synthesized by the chorioepithelium. Embryonal carcinoma contains multiple differentiated extraembryonic structures. It also produces both AFP and HCG. Elevation of these two may be considered for the diagnosis of embryonal carcinoma [12-20]. Embryonal carcinoma is considered the most histogenetically primitive of the germ cell tumors and has the potential to differentiate into mature or immature teratoma. Histologically, this tumor consists of anaplastic columnar to cuboidal cells [21, 22].

Surgery combined with intensive postoperative radiotherapy and chemotherapy is the treatment modalities for embryonal carcinoma [1]. However, the patient survival rate is very low for embryonal carcinoma; the median survival was less than 2 years whereas for the 5 years survival rate was less than 25% [23, 24]. We present 2 cases of intracranial embryonal carcinoma from our center and 13 cases from other literatures. The clinical findings, radiologic findings, surgical treatment and outcomes were summarized to diagnose and consider the treatment modalities for these rare lesions.

**Clinical materials and results**

There were 13 cases which had been reported previously in which the clinical results of each case have been described in the literatures [4, 5, 7, 13, 25-31] and our 2 cases in this report were reviewed (Table 1). All patients were verified histologically as pure embryonal carcinoma. Six Collective studies from other institutions [1, 23, 32-35] were reviewed (Table 2) for comparative study. We analyzed the outcome and treatment strategy to clarify the best combination treatment which can provide better
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prognosis result. Data from 15 reported cases of pure embryonal carcinoma showed that most of the patients have poor prognosis. There were only 3 cases which have survived more than 20 months. In most of cases, patients died within 1 year due to tumor recurrence although they had combination treatment (surgery, radiotherapy and chemotherapy).

Case reports

Case 1

A 5-year-old girl was admitted to our hospital in June 2012 with a 3 days history of paroxysmal headache, nausea and vomiting. The headache was described as dull headache, with no projectile vomiting. Patient had no seizures, no paresis on extremities, or loss of consciousness before admission. Neurologic examination was normal, and funduscopic exploration disclosed a papilledema bilaterally.

CT imaging revealed an isodense posterior third ventricular mass which was responsible for the occlusion of the aqueduct of midbrain and secondary ventricular hydrocephalus. MRI delineated the tumor better, which was located at the posterior third ventricle, with slight hypointense on T1-weighted sequences and displayed strong contrast enhancement [Figure 1]. Cerebrospinal fluid evaluation demonstrated normal levels of α-fetoprotein (AFP; < 0.605 ng/ml) and human chorionic gonadotropin (HCG; 0.29 IU/l). Blood serum evaluation also demonstrated normal levels of α-fetoprotein (AFP; < 0.605 ng/ml) and human chorionic gonadotropin (HCG; 0.1 IU/l).

A ventriculoperitoneal shunting was performed in emergency with immediate postoperative relief. Subsequently, a subtotal surgical resection was achieved via an interhemispheric transcaldosal interforniceal approach. During operation, the tumor was found to be yellowish red solid tumor with calcification; the tumor texture was both soft and tenacious. The tumor had rich blood supply and was quite adhered with surrounding tissue with less clear boundaries. Part of the tumor was tightly adhered with vein of Galen. Tumor specimens showed a
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Histologically aggressive tumor containing epithelial primitive cells forming solid sheets and rare glandular formations [Figure 6]. Immunohistochemical staining was positive for OCT3/4, CD30, CK, Ki-67 [Figure 7]. Based on the typical microscopic findings, the tumor was considered as a pure embryonal carcinoma. Adjuvant high-dose cisplatin-based chemotherapy was administered postoperatively. Later, the patient also had postoperative radiotherapy.

Postoperative MRI scans showed a little tumor remnants [Figure 2A], and the patient had been symptom-free with no clinical or radiological sign of progression at follow-up examination, 6 months after surgery. Unfortunately, the patient died eventually from a pleural effusion caused by lung metastasis of the tumor. Head MRI showed no local tumor recurrence [Figure 2B].

Case 2

A 2-year-old girl was admitted to our hospital in June 2012 with a 1 month history of head tilted to the left and exotropia on the left eye. Patient had headache and vomiting, no seizures, no paresis on extremities or loss of consciousness before admission.

CT imaging revealed an isodense in most of the mass, but there is slight hyperdense in it. The mass was located in the pineal area and responsible for the occlusion of the aqueduct of the midbrain and secondary ventricular hydrocephalus. MRI delineated the tumor better, which was located at the pineal area extended to fourth ventricle; with isointense to slight hypointense on T1-weighted sequences and displayed heterogeneous contrast enhancement [Figure 3], and T2-weighted image showed intratumoral-hemorrhage-like signal [Figure 5A]. Systemic and cerebrospinal fluid evaluation demonstrated normal levels of α-fetoprotein (AFP; 3 ng/ml). Blood serum evaluation also demonstrated normal levels of α-fetoprotein (AFP; 2.51 ng/ml) and human chorionic gonadotropin (HCG; < 1 IU/l).

A ventriculoperitoneal shunting was performed in emergency with immediate postoperative relief. Subsequently, a subtotal surgical resection was achieved via an infratentorial supracerebellar approach. During operation, the tumor was found to be grayish red solid tumor; the tumor texture was both soft and tenacious. The tumor was extended from tegmentum of the midbrain to the fourth ventricle; with isointense to slight hypointense on T1-weighted sequences and displayed heterogeneous contrast enhancement [Figure 3], and T2-weighted image showed intratumoral-hemorrhage-like signal [Figure 5A]. Systemic and cerebrospinal fluid evaluation demonstrated normal levels of α-fetoprotein (AFP; 3 ng/ml). Blood serum evaluation also demonstrated normal levels of α-fetoprotein (AFP; 2.51 ng/ml) and human chorionic gonadotropin (HCG; < 1 IU/l).

Tumor specimens showed a histologically aggressive tumor containing epithelial primitive cells forming solid sheets and glandular formations. Immunohistochemical staining was positive for OCT3/4, CD30, CK, Ki-67, and the tumor was considered as a pure embryonal carcinoma. Postoperative MRI scans showed a little tumor remnants [Figure 4]. Patient did not have
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adjuvant chemotherapy and radiotherapy. Postoperative MRI scans after 3 months showed local tumor recurrence [Figure 5B], and the patient died 6 months after surgery. The cause of death is tumor recurrence.

Discussion

Embryonal carcinoma is a rare malignant intracranial neoplasm. Embryonal carcinomas was first reported by Nishiyama et al and subsequently by Borit et al; the usual locations are tuber cinereum, third ventricle, infundibular region, optic chiasma, suprasellar and intrasellar regions [36, 37]. The theory for embryonal carcinoma origin is remained unclear. In 1946, Friedman and Moore concluded that tumor arises from primordial germ cells that should be called germinomas, and in the following years, they proposed that the embryonal carcinoma was developed from germinoma. According to Dixon and Moore, germ cells gave rise to the germinoma and, alternatively, to the embryonal carcinoma from which the choriocarcinoma and teratoma were derived. Later, Teilum et al summed up the so-called germ cell theory. Germ cell theory explained that germ cells gave rise to germinomas and tumors composed of totipotential cells that gave rise to embryonal carcinomas. This theory also stated that endodermal sinus tumors, choriocarcinomas and teratomas were derived from embryonal carcinomas. Later, this theory was approved by Rubenstein and the World Health Organization committee on brain tumor classifi-
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In 1974, Khantanaphar et al first reported embryonal carcinoma located in the cerebellum. This finding revealed another possibility that the germ cells may migrate through certain tissues before arriving at the gonadal region [4, 38-43]. In 1999, Sano et al proposed another hypothesis, contrary to the above theory. The hypothesis recommended that germ cell tumor is not attributed to one single origin which was the primordial germ cells. According to Sano et al, embryonal carcinoma may arise from the misinvolved-misenfolded cells in earlier stages of embryogenesis (ontogenesis); which was also stated by Matsutani et al [23, 33]. In 2013, Tan and Scotting suggested a novel hypothesis that this tumor arose from the transformation of endogenous brain cells, although future study is needed for clarification [44].

Embryonal carcinoma usually occurs in adolescence and young adult population. Jennings et al suggested that the changes at the time of puberty might induce malignant behavior in germ cells residing in the diencephalopineal region. Thus, gonadotropins would act as transforming agents in this pubertal population. We reported two cases of embryonal carcinoma, both occurred in prepubertal region. Perhaps in this case, the precursor cells required only low level exposure to gonadotropins for transformation; this consideration remains speculative and needs further study to see the gonadotropins relation with this tumor [1].

MRI and CT remain a useful technique for the initial screening, but none of these features could be found to differentiate among germinoma, choriocarcinoma, embryonal carcinoma and yolk sac tumor in the pineal region. Embryonal carcinoma, like most of other germ cell tumors, tends to appear denser than the surrounding brain on the pre- and post-contrast CT scan, and enhances brightly and homogeneously more often than heterogeneously. Chang et al reported that no calcification was noted in embryonal carcinoma [27, 45, 46]. The CT findings in our reported case is inconsistent with above statement; the CT scan results showed isodense and slight hyperdense on pre-contrast CT, and no significance calcification was found. However, there was an interesting finding during operation; we found a small calcification inside the tumor. This is quite unique because most of the calcification can be seen on CT scan. MRI revealed slight hypointense on T1-weighted sequences and both homogenous and heterogeneous contrast enhancement. In one of our cases, the T2-weighted sequences showed intratumoral-hemorrhage-like appearances; this might be a consideration that tumor stroke might occur in embryonal carcinoma since it had rich blood supply.

Increasing level of AFP and HCG may help the diagnosis of this tumor, as reported by many literatures [13-19]. Ushio et al and Matsutani et al also reported high serum levels of AFP and HCG in embryonal carcinoma patient [23, 32]. Inconsistent with these literatures, we found that the CSF and blood serum level of AFP and HCG in our case were normal; our results were consistent with literature reported by Nsir et al. Here we suggested another hypothesis that the elevation of AFP and HCG have relation with age or pre-, during or post puberty condition. We considered this because both patients in our case report were in pediatric population.
and the AFP and HCG level were normal at admission. As from this data we thought that AFP and HCG level in children embryonal carcinoma might be different with the young and adult population. Further study needs to be done, including retrospective and collective study, to answer this question. AFP and HCG level alone cannot confirm the diagnosis for embryonal carcinoma. Therefore, these are important to consider whether preoperative chemotherapy and radiotherapy should be given. We had recommended for patients in our institution diagnosed with other types of germ cell tumors whom have elevation in AFP and HCG to have preoperative chemotherapy and radiotherapy; the result was both AFP and HCG level were decreasing after the treatment, and it’s consistent with other reported literatures [47].

Hydrocephalus and Parinaud’s syndrome generally present in posterior third ventricle and pineal area tumor. Two patients in our cases were presented with hydrocephalus and we performed ventriculoperitoneal shunt prior to surgery to relieve the intracranial pressure; one of the patients had Parinaud’s syndrome. The placement of ventriculoperitoneal shunt might benefit surgical treatment. In high intracranial pressure condition, rapid drop of the blood pressure and cerebral or cerebellar bulging may occur during surgery and sudden decompression after dural opening might increase the surgical morbidity and mortality. Surgical approach might include occipital transfenestorial or frontal transcallosal; infratentorial supracerbellar approach is generally used in patients with pineal tumors, and the ptorial approach of subfrontal approach is preferred in patients with sellar region tumors. For posterior third ventricle and pineal region, most of the tumor has intimate relationship with the posterior thalamus and deep cerebral veins, such as internal cerebral veins and vein of Galen. Because of this complex anatomical structure, we do not recommend any stereotactic biopsy. Despite its disadvantageous location, the tumor mostly had a clear anatomic boundary with surrounding normal tissue so in most cases subtotal to total resection can be achieved [48-51]. In our presented cases we performed transcallosal approach for the tumor located in the posterior third ventricle and infratentorial supracerbellar approach for tumor located in pineal area extended to the fourth ventricle. Under surgical microscope, the tumor had less clear boundaries and tightly adhered with surrounding normal tissue which had rich blood supply. We achieved subtotal resection in both our cases. CD30-positive staining basically can confirm the diagnosis of embryonal carcinoma, but evidence from recent studies showed that new immunostains such as organic cation transporter 3/4 (OCT3/4) had a better sensitivity and specificity than CD30 [52, 53]. In our case, the combination of specific microscopic findings, OCT3/4, CD30, CK and Ki-67 positively led to the diagnosis of pure embryonal carcinoma.

The efficacy of radiotherapy and chemotherapy remains a topic of controversy. Nevertheless, most patients still receive those treatments. The tumor may extend via three different pathways: direct continuity, seeding via the CSF and occasionally via the blood stream. Whole radiotherapy can be considered because of the malignant characteristic of the tumor that disseminate through CSF; chemotherapy might be considered in patient who has a delayed craniospinal irradiation or in average risk patients, and in young patients especially less than 3 years old [45, 54, 55]. Besides, adjuvant chemotherapy might reduce the radiotherapy doses. The usual chemotherapy regimen which is generally used in NGGCT is PVB (cisplatin/ vinblastine/bleomycin) combination. Robertson et al reported that the 4 year progression-free survival rate was 67% [34]. German/Italian pilot study treated 19 NGGCT patients with neoadjuvant chemotherapy (cisplatin/etoposide/ifosfamide) followed by radiation therapy. Preliminary results revealed an 81% progression-free survival rate at 12 months. Jennings and Balcomanda attempted to use single-modal therapy with radiation therapy alone or chemotherapy alone; the results were at unacceptably high recurrence rate [1, 35, 36]. French pilot study used 6 cycles of multiagent chemotherapy alone and deferral of radiotherapy; the results were relapse of the tumor [56]. Later, a study conducted by Japanese Intracranial Germ Cell Tumor Study Group using PE (cisplatin and etoposide) had showed promising result for primary intracranial yolk sac tumors or embryonal carcinoma. The objectives of this
therapy are to reduce the tumor volume, therefore minimizing the side effects of surgery, and decrease the viability of tumor cells to prevent CSF metastasis. The result of this study was identical to that reported by Robertson et al [34]. On the contrary, Matsutani et al showed that embryonal carcinoma patient had 3 year survival rate of 27.3%; less than the result reported by Ushio and Robertson. Matsutani reported that extensive surgery might be beneficial to reduce the recurrence, compared to partial removal, and chemotherapy was not significantly more effective than radiation therapy alone [23, 57]. In our cases, both patients did not have good prognosis; one of the patient died 1 year after surgery combined with post-operative cisplatin-based chemotherapy and radiotherapy. The other patient had worse prognosis and due to the patient’s age of younger than 3 years old, we did not recommend chemotherapy and radiotherapy; the patient died 6 months later due to local recurrence of the tumor. Our reported case is consistent with Matsutani report.

Disclosure of conflict of interest

None.

Address correspondence to: Chunde Li, Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing 100050, China. Tel: +86-13366077663; E-mail: lichunde@hotmail.com

References

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