Neoadjuvant chemotherapy for newly diagnosed germ-cell tumors of the central nervous system

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A neoadjuvant (preradiotherapy) chemotherapy regimen consisting of either cyclophosphamide alone (60 to 80 mg/kg) or a modified multidrug regimen (vinblastine, bleomycin, cyclophosphamide, and cisplatin) was administered to 15 newly diagnosed patients with histologically confirmed, fully staged, primary germ-cell tumors (GCT's) of the central nervous system (CNS). There were 11 patients with germinomas and four with non-germinoma malignant GCT's. There were six females and nine males, whose median age was 13 years (range 4 months to 24 years). Seven germinoma patients (64%) had disseminated disease. For the germinoma patients, the subsequent radiotherapy dose was modified based on the response to the neoadjuvant chemotherapy, and craniospinal radiotherapy was given only to those with disseminated CNS disease at diagnosis. Ten of the 11 germinoma patients had complete disappearance of all evaluable disease after two courses of chemotherapy (cyclophosphamide in eight and multidrug in three) and one had a partial response. The planned dose of radiotherapy to the primary tumor was reduced from 5500 to 3000 rads, and the craniospinal dose was lowered from 3600 to 2000 rads. Ten patients remain in continuous disease-free remission 20+ to 89+ months after diagnosis (median follow-up period 47 months). All four patients with non-germinoma GCT's received the multidrug regimen, and two of three patients with evaluable disease had a partial response. High-dose regional and craniospinal radiotherapy was administered thereafter, but only two patients remain in their first remission.

Previously untreated germinoma is a highly chemosensitive disease and the neoadjuvant treatment strategy permits the identification of active chemotherapy regimens in newly diagnosed patients. Patients who have complete responses to neoadjuvant chemotherapy tolerate a significant radiotherapy dose reduction without compromising long-term survival, thereby allowing a reduction of some of the late effects of therapeutic radiation. Germinomas tend to disseminate early in the course of the disease and a pre-therapy staging evaluation permits individualized radiotherapy treatment planning.

KEY WORDS • brain neoplasm • chemotherapy • germinoma • germ cell tumors • radiation therapy

GERM-CELL tumors (GCT's) of the central nervous system (CNS) constitute an uncommon, biologically diverse group of primary brain tumors with varying radiosensitivity, arising primarily in the pineal or suprasellar regions. They comprise less than 5% of childhood primary brain tumors.9 Only 30 to 40 new cases are expected to arise in children each year in the United States.15 The most common variant, the germinoma, is highly radiosensitive and potentially radiocurable. Nevertheless, 5-year recurrence rates for germinomas range from 10% to 40% in several large institutional series.10,14,17 Conventional therapy usually consists of high-dose radiotherapy (> 5000 rads) following a clinically suspected and/or biopsy-confirmed diagnosis of a pineal region germinoma.

Recently, the neurosurgical morbidity and mortality associated with an operative approach to the pineal and suprasellar regions have been significantly reduced by the use of perioperative steroids, antidiuretic hormones, and microneurosurgical techniques. Thus, histological diagnoses are being obtained with increasing frequency,6 permitting the rational development of histology-specific therapy. It is becoming increasingly apparent that GCT's may not comprise the major histological category in contemporary pediatric operative series of biopsy-proven pineal region tumors.13 Protocols are needed to determine the minimum radiation dose and volume sufficient for the cure of patients with germinomas, the value of chemotherapy for this highly radiosensitive disease, and the late effects
### TABLE 1
Clinical summary in 15 patients with germ-cell tumors*

<table>
<thead>
<tr>
<th>Case No. &amp; Sex</th>
<th>Prodrome &amp; Location of Tumor</th>
<th>Measurable Disease</th>
<th>Neoadjuvant Chemotherapy</th>
<th>RT Dose (rads)</th>
<th>Survival (mos)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Drug</td>
<td>No. of Courses</td>
<td>Local Craniospinal Disease-Free Total</td>
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<td></td>
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<td>Do (mg/kg)</td>
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<td>localized germinoma</td>
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<td>1 10, F</td>
<td>36 suprasellar</td>
<td>CT</td>
<td>C 100</td>
<td>2 complete</td>
<td>3000</td>
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<tr>
<td>2 13, F</td>
<td>4 suprasellar</td>
<td>CT</td>
<td>C 60</td>
<td>2 complete</td>
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<td>3 14, F</td>
<td>41 suprasellar</td>
<td>CT</td>
<td>C 60</td>
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<td>4 14, M</td>
<td>12 suprasellar</td>
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<td>C 60</td>
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<td>disseminated germinoma</td>
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<td>5 15, F</td>
<td>9 pineal &amp; suprasellar</td>
<td>CT: multiple lesions</td>
<td>VAB</td>
<td>2 complete</td>
<td>3600</td>
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<tr>
<td>6 12, M</td>
<td>4 pineal</td>
<td>CT: pineal; CSF</td>
<td>C 80</td>
<td>2 complete</td>
<td>3000</td>
</tr>
<tr>
<td>7 9, F</td>
<td>19 suprasellar</td>
<td>CT: multiple lesions</td>
<td>C 80</td>
<td>2 complete</td>
<td>4500</td>
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<tr>
<td>8 15, M</td>
<td>1 pineal</td>
<td>CT: suprasellar lesion; myelogram: caudal equina; CSF</td>
<td>VAB</td>
<td>1 complete</td>
<td>3000</td>
</tr>
<tr>
<td>9 9, F</td>
<td>48 suprasellar</td>
<td>CT: suprasellar lesion; myelogram: caudal equina; CSF</td>
<td>C 60</td>
<td>2 complete</td>
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<td>10 24, M</td>
<td>6 pineal</td>
<td>CT: pineal; CSF</td>
<td>C 60</td>
<td>2 mixed</td>
<td>4500</td>
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<td>11 16, M</td>
<td>½ pineal</td>
<td>CT: pineal; myelogram: caudal equina; CSF</td>
<td>C 60</td>
<td>2 mixed</td>
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<td>malignant teratoma</td>
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<td>12 ½, M</td>
<td>1 4th ventricle</td>
<td>CT</td>
<td>VAB modified for age</td>
<td>2 progressive disease</td>
<td>4500</td>
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<tr>
<td>13 7, M</td>
<td>1 pineal</td>
<td>CT</td>
<td>VAB modified for age</td>
<td>2 disease</td>
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<tr>
<td>14 13, M</td>
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<td>CT: pineal</td>
<td>VAB</td>
<td>2 partial</td>
<td>5500</td>
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<td>15 3, M</td>
<td>9 parietal</td>
<td>CT</td>
<td>VAB</td>
<td>2 partial</td>
<td>5500</td>
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*R = radiotherapy; CT = computerized tomography; CSF = cerebrospinal fluid cytological examination; C = cyclophosphamide; VAB = vinblastine, bleomycin, cisplatin, and cyclophosphamide multidrug therapy.

† Age at diagnosis.

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of therapy in long-term survivors. Patients with the radioinsensitive non-germinoma GCT's such as embryonal carcinoma, endodermal sinus tumor, choriocarcinoma, and malignant teratoma have a much poorer prognosis.6,11,13

Because GCT's are uncommon, we have only been able to conduct an exploratory study at an institutional level utilizing a new treatment strategy, “neoadjuvant” or preradiation postoperative chemotherapy. Our goals for the two groups of intracranial GCT's differ: for germinoma patients our aim is to lessen the late effects of high-dose radiotherapy by adding chemotherapy and lowering the dose of radiotherapy; for non-germinoma GCT patients, our goal is to improve survival rates by adding multidrug chemotherapy to high-dose radiotherapy. The validity of these approaches can only be determined in randomized trials. This report presents the results of a nonrandomized pilot study in 15 newly diagnosed, serially accessioned fully-staged patients with primary intracranial GCT's who underwent a neoadjuvant phase II chemotherapy trial.

**Clinical Material and Methods**

**Patient Population**

Fifteen patients with histologically confirmed primary intracranial GCT's participated in this study (Table 1). The median age was 13 years (range 4 months to 24 years). There were six females and nine males. Thirteen patients were treated at Memorial Sloan-Kettering Cancer Center and two patients (Cases 11 and 14) were treated at the Children's Hospital of Philadelphia. Eleven had pure germinomas and four had non-germinoma GCT's. The site of origin of the tumor in the 11 germinoma patients was suprasellar in six, pineal in three, and suprasellar plus pineal in two. The non-germinoma GCT's included two malignant teratomas (one pineal and one in the fourth ventricle), one mixed pineal GCT (germinoma and embryonal carcinoma), and one parietal endodermal sinus tumor. Five of the six patients with a suprasellar primary tumor were female. All seven patients with a primary tumor in the pineal region were male.

The interval between onset of symptoms and surgical diagnosis varied depending on the primary location of the tumor. For the six patients with suprasellar primary tumors, the median interval was 36 months (range 4 to 48 months). The initial symptom was diabetes insipidus in all six of these patients, followed in temporal order by growth failure in three, visual disturbances in four, and panhypopituitarism in one. Of the four patients with localized suprasellar germinomas, three underwent computerized tomography (CT) scanning 29, 29, and
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40 months, respectively, before diagnosis to evaluate the cause of diabetes insipidus. These initial CT scans were all normal. The symptomatic period before diagnosis was considerably shorter (median 1 month, range 2 weeks to 6 months) in the five patients with primary tumor in the pineal region. Of these patients, two with the longest symptomatic intervals (4 and 6 months) had germinomas and presented with diabetes insipidus 4 and 6 months prior to surgery. The CT scans at that time revealed only pineal region disease. The other three patients with pineal region tumor presented with symptoms of raised intracranial pressure and had symptoms for a month or less.

Surgery consisted of a biopsy or subtotal resection in 14 patients and a gross total resection in one child with a malignant teratoma of the pineal region. Stereotaxic biopsies were performed in two patients with pineal region tumors, and direct operative approaches were made in the other 13. Six of the patients, five of whom had primary tumors arising in the pineal region, required ventriculoperitoneal shunt placement prior to a craniotomy.

All patients were studied with a chest x-ray film, a postoperative CT scan obtained without and with infusion of contrast medium to document residual tumor and/or intracranial metastases, a metrizamide myelogram, cytological examination of several lumbar and, if possible, ventricular cerebrospinal fluid (CSF) samples, and analysis of serum and CSF tumor markers including alpha-fetoprotein, the beta subunit of human chorionic gonadotropin, and carcinoembryonic antigen. Seven of the 11 germinoma patients had evidence of CNS dissemination, including multiple lesions on CT, subarachnoid metastases on myelography, and/or tumor cells in the CSF. Multiple intraventricular metastases were apparent in three germinoma patients. The CSF cytological examinations identified clumps of malignant cells in four of the 11 patients with germinomas, but were normal in all four patients with non-germinoma GCT's.

Treatment Plan

The type of neoadjuvant chemotherapy was determined in large measure by the tumor histology. The protocol required that patients with pure germinomas receive a single intravenous (IV) drug: high-dose cyclophosphamide (1800 mg/sq m given in two consecutive split daily doses of 900 mg/sq m/day). Patients with non-germinoma GCT's or mixed GCT's were given the following modified version of the vinblastine, bleomycin, cisplatin, and cyclophosphamide multidrug therapy (VAB) protocol, in which actinomycin D was eliminated and the dose of cyclophosphamide was increased from 600 to 900 mg/sq m. This latter regimen was administered as follows: Day 1: cyclophosphamide (900 mg/sq m IV), vinblastine (4 mg/sq m IV), and bleomycin (15 mg/sq m by IV push); Days 1 to 3: bleomycin (20 mg/sq m/day by continuous IV infusion); and Day 4: cisplatin (120 mg/sq m IV), with mannitol-enforced diuresis. Exceptions were made in the execution of therapy during the formative stages of the protocol. For example, three patients with germinomas received the unmodified version of the VAB protocol including actinomycin D rather than high-dose cyclophosphamide.

Two courses of either the single-drug or multidrug chemotherapy were given. Thereafter, a response determination was made by repeating those diagnostic tests that originally identified the evaluable disease. Standard response criteria were utilized for patients with measurable disease. The fluid and electrolyte balance was carefully monitored in all patients. Since high-dose cyclophosphamide may induce a mild antidiuretic hormone effect, the dose for those patients receiving DDAVP (desmopressin acetate) was withheld for 12 hours after chemotherapy infusion. All patients treated with high-dose cyclophosphamide received transfusions when necessary with irradiated blood products to prevent graft versus host reactions.

The radiation therapy was planned taking into account the tumor histology, the results of examinations prior to chemotherapy, and the response to the neoadjuvant chemotherapy. Patients with localized germinomas received only regional radiotherapy. If a complete response or complete disappearance of all evaluable disease was observed after chemotherapy, then the radiation dose was reduced to 3000 rads delivered over 4 weeks. If less than a complete response to chemotherapy was observed, then 5000 rads of regional radiotherapy delivered in 160- to 180-rad daily fractions over 5 to 6 weeks would be administered to a regional port.

In cases of disseminated germinomas, craniospinal radiotherapy was added to the protocol. If a complete response was detected, the craniospinal dose was reduced from 3600 to 2000 rads and the regional dose from 5000 to 3000 rads. Patients older than 3 years who had localized or disseminated non-germinoma GCT's received high doses of regional (5000 rads) and craniospinal therapy (3600 rads) with focal boosts to areas of metastatic disease, regardless of their response to chemotherapy.

After completion of radiotherapy, the patients were followed with neurological examinations, CT scans, CSF cytological examination, and analysis of CSF tumor markers. Their endocrine status was monitored closely by a pediatric endocrinologist. After radiother-
apy no further chemotherapy was given to patients who remained in continuous remission.

Results

Response to Preradiation Chemotherapy

Objective responses to chemotherapy were detected in all germinoma patients and in two of the three non-germinoma GCT patients with evaluable disease (Table 1). In 10 of the 11 germinoma patients, all measurable disease completely disappeared after two courses of chemotherapy, constituting a complete response. Cyclophosphamide was used in eight cases and VAB in three cases. In one germinoma patient with disseminated disease (Case 11), a complete disappearance of the pineal tumor was documented on CT, but the CSF cytological examination continued to manifest tumor cells.

Two patients with non-germinoma GCT's (Cases 14 and 15) had CT evidence of a partial response after two courses of the VAB protocol. The infant with the fourth ventricular malignant teratoma (Case 12) failed to respond to neoadjuvant VAB or to subsequent radiotherapy, and died of locally recurrent disease.

Radiotherapy

The planned dose of radiotherapy was modified in the 10 patients with germinoma who had a complete response to chemotherapy. The mean tumor dose in these patients was reduced from 5500 to 3310 rads (range 3000 to 4500 rads), a 40% dose reduction. For the seven germinoma patients with disseminated disease, the mean craniospinal dose was reduced from 3600 to 2620 rads (range 2000 to 3000 rads), a 27% dose reduction. One patient with a disseminated germinoma who had a mixed response to chemotherapy (Case 11) and the three older non-germinoma patients (Cases 13, 14, and 15) received a full 5500-rad dose of radiotherapy to the tumor, and three of these received craniospinal therapy as well. Radiotherapy was begun an average of 4 weeks after the last dose of chemotherapy. There was no unusual acute toxicity or delay in radiotherapy delivery that could be attributable to the prior chemotherapy.

Survival

Twelve of the 14 patients with evaluable disease were long-term survivors (beyond 12 months); one of these (Case 15) has recently completed a course of radiotherapy. Ten of the 11 germinoma patients remain in continuous disease-free remission and one has died. The median follow-up period for the 10 germinoma patients evaluable for survival is 47+ months (range 23+ to 89+ months). Two of the four patients with non-germinoma GCT’s (Cases 13 and 15) remain in continuous disease-free remission for 21+ and 12+ months, respectively, and another (Case 14) is responding to retrieval VAB chemotherapy 21+ months after diagnosis and following a relapse at 9 months.

Discussion

Primary intracranial GCT's constitute 0.5% to 3% of brain tumors diagnosed in large institutional series. Although there are several histological variants, the germinoma is the most common type, comprising over 50% of GCT cases. Prior to the 1970's the germinoma's high radiosensitivity was used to test a presumptive diagnosis before surgery; if a therapeutic radiotherapy trial was successful, the patient was spared the hazards of surgery. Germinomas were observed to respond clinically following 2 to 3 weeks of radiotherapy. Relatively high radiation doses (> 5000 rads) and large volumes (to the whole brain or to craniospinal ports) were commonly administered later to consolidate therapy. The 5-year survival rates for surgically confirmed cases of germinoma have ranged from 60% to 90%; however, recurrences later than 5 years after the original diagnosis have also been noted.

Germinomas tend to arise in older children and young adults. Since many of these youthful patients...
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may anticipate a favorable prognosis, they are at high risk for acquiring late effects of their treatment, such as neuroendocrine and cognitive deficiencies related in part to the high doses and large volumes of radiotherapy. Although dysgerminomas and seminomas (histologically similar tumors arising elsewhere in the body) have been cured with significantly lower doses of radiation (range 2500 to 3000 rads), radiation oncologists have been reluctant to reduce the dose and volume for germinoma cases, where the prognosis may be less favorable.

A variety of tumors arise in the pineal region, including low-grade and fully malignant tumors. Choice of the radiotherapy plan and selection of specific chemotherapy drugs can best be made when the histological diagnosis is known, as in all of our patients. The differential diagnosis of pineal region masses differs in each decade of life; GCT's predominate in the second and third decades and other tumors, such as pineocytomas or pineoblastomas and gliomas, are relatively more common in other decades.

Chemotherapy is effective in patients with recurrent germinomas and in newly diagnosed and recurrent seminomas. For example, chemotherapy alone or combined with radiotherapy has produced cure rates in excess of 80% for newly diagnosed localized and metastatic seminomas. The chemotherapy regimens used in our protocol were selected because of our prior experience in treating recurrent GCT's of the CNS, and because of the known sensitivity of systemic GCT's to alkylating agents such as cyclophosphamide and the multiagent VAB regimen. High rather than conventional doses of cyclophosphamide were used to enhance blood-brain barrier penetration, and a favorable result has been achieved with this regimen with other primary brain tumors, such as medulloblastoma. The VAB regimen has been modified by eliminating actinomycin D while increasing the dose of cyclophosphamide from 600 to 900 mg/sq m.

Newly diagnosed intracranial germinomas are very responsive to chemotherapy alone when administered prior to radiotherapy. Of our 11 germinoma patients, seven of eight who received cyclophosphamide alone and all three who received the VAB regimen showed complete disappearance of all measurable disease after only two monthly courses of chemotherapy. Although there are some theoretical reasons to support a multiagent chemotherapy regimen such as the VAB protocol, cyclophosphamide alone was selected for germinomas because of its high activity and lower toxicity.

A relatively high incidence of CNS metastases was revealed at diagnosis in the germinoma patients with such neurodiagnostic methods as CT, myelography, CSF cytology, and tumor markers. Multifocal CT lesions and abnormal CSF cytological examinations have been reported with variable frequency in prior studies. Seven (64%) of our 11 patients were found to have CNS metastases prior to therapy, including multiple lesions on CT in three, filling defects on myelography in two, and abnormal CSF cytological findings in three. Only one of these patients (Case 11) had asymptomatic metastasis.

All seven patients with disseminated germinomas received craniospinal radiation treatment in addition to higher doses directed to their metastatic lesions. The development of CNS disease outside regional radiation fields has been noted in 10% to 57% of cases at the time of relapse in large institutional series. Sung, et al., have advocated the routine use of craniospinal ports for all patients. They noted that eight (57%) of 14 germinoma patients treated with high-dose regional radiotherapy developed cerebral or spinal metastases within 3 years of diagnosis. We believe that the relatively high incidence of subclinical CNS dissemination at diagnosis observed in our study justifies the routine performance of a staging examination prior to therapy. Craniospinal radiotherapy should be administered to all patients when irradiation is the only treatment modality, and metastatic lesions should receive a radiation boost; however, our present approach using neoadjuvant multimodal chemotherapy is to administer craniospinal radiation therapy only to those germinoma patients with CNS metastases documented at diagnosis.

There is concern that high radiotherapy doses in the range of 5000 to 5500 rads may be excessive for germinomas. Long-term disease control has been achieved in some studies with lower doses. In a single-arm pilot study such as ours, it was difficult to justify a dose reduction without adding another effective treatment such as chemotherapy. The 10 patients who responded completely to neoadjuvant chemotherapy received a lower dose of radiotherapy, with a mean tumor dose of 3300 rads and a mean craniospinal dose of 2620 rads. Although the follow-up period is still relatively short and germinomas may recur late, our survival data compare favorably with the best published figures. Only one of our 11 germinoma patients who had a complete response to chemotherapy developed a recurrence following a reduced regional radiotherapy treatment plan.

With a rare tumor such as the germinoma, insights regarding the role of specific chemotherapy regimens can be made based on the neoadjuvant chemotherapy strategy. The theoretical advantages of this approach include: the documentation of responses to specific chemotherapy regimens in newly diagnosed disease prior to radiotherapy; the possible synergistic interaction with subsequent radiotherapy; the control of occult systemic metastases; and (in cases where a favorable response to chemotherapy is observed) the option to modify the planned course of radiotherapy with a view to reducing some late radiation-induced brain damage. The true benefit of any adjuvant chemotherapy regimen in terms of prolongation of survival can only be determined in a randomized clinical trial in newly diagnosed patients.

It cannot be concluded from this single-arm study of germinoma patients that reduced doses of radiotherapy...
lessen late damage to the brain, as determined by the assessment of neuroendocrine and cognitive performance. This would require prospective monitoring of late effects in a randomized study of two radiotherapy doses; however, data are available from other studies showing late radiation dose-related brain injury and the increased susceptibility of younger patients.7,12,16

The management of non-germinoma GCT’s of the CNS, such as malignant teratomas, endodermal sinus tumors, embryonal carcinomas, and/or choriocarcinomas, requires a different therapeutic strategy. The major concern is to prolong survival rather than the late effects of therapy. These tumors are relatively radioresistant and the prognosis following high doses and volumes of radiotherapy is poor.11 There is a compelling justification for adding chemotherapy to the management of these tumors for several reasons. Tumors with similar histological features that arise in other parts of the body are curable with a multimodal treatment strategy employing maximum surgical resection followed by multiagent chemotherapy such as the VAB or Einhorn regimen and regional radiotherapy.18 Furthermore, there is evidence that recurrent CNS non-germinoma GCT’s respond to single-agent and multiagent chemotherapy, although not as readily as germinomas.2 Our experience with multimodality therapy in newly diagnosed patients for this group of tumors is limited (that is, four cases including three with measurable disease). Two children had partial responses to the modified VAB regimen after two courses. The neoadjuvant chemotherapy strategy also has merit for patients with these tumors for the reasons stated above.

The optimum number of courses and whether to add postirradiation chemotherapy for this group of poor-risk patients are issues to study further, especially in cases where a chemotherapy regimen is shown to be useful prior to radiotherapy. Several more courses of a regimen like the VAB could probably be given after craniospinal radiotherapy, with modifications for toxicity. Thus, our present management of suprasellar and pineal region lesions includes: 1) surgical diagnosis to confirm the presence of a GCT; 2) a staging evaluation, including postoperative CT, myelography, CSF cytological examination, and serum and CSF tumor markers; 3) administration of neoadjuvant chemotherapy (cyclophosphamide for pure germinoma and the modified VAB regimen for non-germinoma GCT’s); and 4) radiotherapy dose reductions for germinoma patients depending on the presence of CNS metastases and the response to chemotherapy, but full regional and craniospinal doses of radiotherapy for malignant non-germinoma GCT’s. Given the rarity of this group of CNS tumors and their varied histology, the optimum management must be determined in the context of controlled, randomized clinical trials conducted by large cooperative groups.

Acknowledgments
The authors acknowledge the contributions of Berta Jereb, M.D., and Russell Walker, M.D., in the conduct of this study.

References


J. C. Allen, J. H. Kim and R. J. Packer