Intracranial Germ Cell Tumors

ROGER J. PACKER, a BRUCE H. COHEN, b KATHLEEN CONEY c

a Center for Neuroscience and Behavioral Medicine, Department of Neurology, Children’s National Medical Center; Department of Neurology and Pediatrics, The George Washington University, Washington, DC and Department of Neurosurgery, University of Virginia, Charlottesville, Virginia, USA; b Department of Pediatric Neurology and the Brain Tumor Center, Cleveland Clinic Foundation, Cleveland, Ohio, USA; c Center for Neuroscience and Behavioral Medicine, Department of Neurology, Children’s National Medical Center, Washington, DC, USA

Key Words. Intracranial germ cell tumor · Germinoma · Mixed germ cell tumor · Nongerminomatous germ cell tumor · Chemotherapy · Radiation therapy · Embryonal carcinoma · Teratoma

ABSTRACT

Intracranial germ cell tumors are a heterogeneous group of lesions which occur in children and adults. Within the classification of intracranial germ cell tumors, there are a variety of different tumor types which carry different prognoses. The diagnosis of an intracranial germ cell tumor usually requires histological information, but a subgroup of tumors will secrete specific tumor markers, including α-fetoprotein and β-human chorionic gonadotropin, which may obviate the need for surgical intervention.

The management of intracranial germ cell tumors in both children and adults remains unsettled. Germinomas have a good prognosis, as over 90% of patients can be effectively treated with radiation therapy. The dose and volume of radiation therapy needed for disease control is not well established, and controversy exists concerning the need for whole brain or craniospinal radiation therapy for localized tumors. Germinomas are also chemosensitive and recent reports suggest that the dose and volume of radiation therapy required for disease control can be lessened with the addition of adjuvant chemotherapy.

The outcome for patients with nongerminomatous germ cell tumors is less favorable. Radiation therapy alone will result in disease control in 40%-60% of patients. The addition of chemotherapy to radiation therapy may improve the rate of survival. The Oncologist 2000;5:312-320

INTRODUCTION

Intracranial germ cell tumors are a heterogeneous group of lesions which arise in patients of all ages. Due to the morbidity associated with surgery of pineal region tumors and the variability in classification schemas utilized to characterize such lesions, the exact incidences of specific types of germ cell tumors are difficult to determine [1]. Intracranial germ cell tumors vary in their geographic incidence; in Western series, they constitute anywhere between 0.4% and 3.4% of patients with primary central nervous system (CNS) tumors, while in series reviewing patients in Japan and the Far East, the incidence of germ cell tumors is five- to eightfold greater [1-3]. This greater incidence of CNS tumors parallels the greater frequency of testicular germ cell tumors in Japan compared to the United States.

Germ cell tumors most frequently arise in the pineal and suprasellar region and, in general, pineal region germ cell tumors outnumber suprasellar tumors by a ratio of 2:1 [1, 4]. At the time of diagnosis, between 5%-10% of germ cell tumors are found both in the suprasellar and pineal region [1]. This bifocal disease occurs primarily in patients with germinomas, and it is unclear whether it represents actual spread of the tumor or the simultaneous development of tumors in two sites. Germ cell tumors will also occur in other regions of the brain, with a tendency to arise in the midline, including tumors of the fourth ventricle, basal ganglionic region, and thalamus. In general, germ cell tumors which arise in the basal ganglionic region or the thalamus are more likely to be germinomas, rather than other forms of germ cell tumors.

Males are approximately two times more likely than females to develop germ cell tumors [1]. This male-to-female ratio is higher for nongerminomatous germ cell tumors [5]. The male predominance of germinomas is primarily limited to...
the pineal region, as suprasellar germinomas are more frequent in females. Germ cell tumors peak in incidence near the time of puberty. Nongerminomatous germ cell tumors are more frequently diagnosed earlier in life, while germinomas are usually diagnosed between 10 and 21 years of age [1, 5].

CLASSIFICATION

The classification of the germ cell tumors has not been uniform. One classification schema is based on the concept, proposed by Teiium, that all germ cell tumors are derived from a primordial germ cell, and they either differentiate into a germinoma or, through totipotential cells, give rise to other types of germ cell tumors [6]. The embryonal carcinoma is considered a critical branch point for nongerminomatous cell tumors, and depending on the interaction of this cell with other types of tissue in the area, the tumor will differentiate into a choriocarcinoma, an endodermal sinus tumor, or a teratoma.

Takei and Pearl have suggested an alternative classification schema, based on the concept that the fetal yolk sac is the origin of primordial germ cells, and tumors may develop along a variety of different cell lines [7]. Sano and colleagues have suggested that the germinoma is the only neoplasm arising from the germ cell, while other so-called germ cell tumors are dysembryogeneic and are misinvolved-misfolded into the lateral mesoderm and carried into a variety of different brain regions [8]. The most recent World Health Organization classification of germ cell tumors is as noted in Table 1 [9]. Classifications are subjective and are also highly dependent on tumor sampling, especially when only biopsies are performed. More recently, histological diagnosis has been supplemented by evaluation of tumor markers.

TUMOR MARKERS

The presence, or absence, of specific protein markers, produced and/or secreted by tumor cells, has been an extremely important adjunct in the diagnosis of germ cell tumors [10]. At high levels, these protein markers can be measured in the serum, although cerebrospinal fluid levels are a more sensitive and reliable measure of tumor presence [10]. The usual pattern of tumor marker secretion in germ cell tumors is outlined in Table 2. α-fetoprotein is a yolk cell marker and is present in endodermal sinus tumors. β-human-chorionic-gonadotropin (β-HCG) is produced by normal trophoblastic tissue in the placenta, and by choriocarcinomas [11]. Low levels of β-HCG have been detected in a variety of tumors, and it may be a nonspecific marker of malignancy [12]. This may limit the diagnostic specificity of β-HCG for choriocarcinomas and nongerminomatous germ cell tumors. A mild elevation of β-HCG has been noted in the syncytiotrophoblastic form of germinoma. Placental alkaline-phosphatase is a relatively nonspecific germ cell tumor marker and is not particularly useful in diagnosing the specific type of germ cell tumor present [13].

CLINICAL PRESENTATION

Clinical presentations of germ cell tumors are dependent on the location of the tumor in the CNS, the size of the lesion and age of the patient. The anatomic relationship between the pineal gland and the quadrigeminal plate, third ventricle and deep venous structures accounts for most of the symptoms associated with pineal region tumors [1, 14]. Germ cell tumors in the pineal region, independent of histological subtype, most commonly present with hydrocephalus, a remarkable constellation of visual symptoms (including failure of upper gaze, pupils which react better to accommodation than light, lid retraction, and convergence or retraction nystagmus—Parinaud’s Syndrome), obtundation, pyramidal tract signs, and ataxia. Patients with germinomas are equally likely to present with hydrocephalus and obtundation or Parinaud’s Syndrome [1, 14]. Patients with nongerminomatous germ cell tumors tend to have larger tumors and more severe neurologic compromise at the time of diagnosis, including a higher incidence of hydrocephalus and visual dysfunction.

<table>
<thead>
<tr>
<th>Table 1. WHO classification of intracranial germ cell tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0 Germ cell tumors</td>
</tr>
<tr>
<td>5.1 Germinomas</td>
</tr>
<tr>
<td>5.2 Embryonal carcinoma</td>
</tr>
<tr>
<td>5.3 Yolk sac tumor</td>
</tr>
<tr>
<td>5.4 Choriocarcinoma</td>
</tr>
<tr>
<td>5.5 Teratoma</td>
</tr>
<tr>
<td>5.5.1 Immature</td>
</tr>
<tr>
<td>5.5.2 Mature</td>
</tr>
<tr>
<td>5.5.3 Teratoma with malignant transformation</td>
</tr>
<tr>
<td>5.6 Mixed germ cell</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2. Cerebrospinal fluid markers in germ cell tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teratoma</td>
</tr>
<tr>
<td>Germinoma (Pure)</td>
</tr>
<tr>
<td>Germinoma (syncytiotrophoblastic)</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
</tr>
<tr>
<td>Mixed germ cell</td>
</tr>
<tr>
<td>Endodermal sinus</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>β-HCG</th>
<th>α-FP</th>
<th>PLAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>± (weak)</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>++</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>++</td>
<td>++</td>
<td>±</td>
</tr>
<tr>
<td>±</td>
<td>++</td>
<td>±</td>
</tr>
<tr>
<td>±</td>
<td>±</td>
<td>±</td>
</tr>
</tbody>
</table>

Legend

β-HCG = beta-human-chorionic gonadotropin
α-FP = alpha-fetoprotein
PLAP = placental alkaline-phosphatase
Suprasellar germinomas usually present with evidence of hypothalamic/pituitary dysfunction, which most commonly includes diabetes insipidus but may also include delayed sexual development, hypopituitarism and/or isolated growth failure [1, 15]. Up to 35% of patients with suprasellar tumors will be asymptomatic for more than six months, and in this subgroup of patients, the time between first symptom and diagnosis may be prolonged. This is especially true for those patients with isolated diabetes insipidus or isolated difficulties with growth or the onset of puberty. The cause of precocious puberty in patients with pineal region tumors is only partially understood [1, 16]. This symptom may arise in 5% of patients with pineal and/or hypothalamic tumors. β-HCG and luteinizing hormone levels may be elevated in some patients with precocious puberty, and choriocarcinomas are more likely to present with precocious puberty than any other type of germ cell tumor. Diabetes insipidus has also been found in patients with isolated, or apparently isolated pineal region tumors [1, 14]. Some have suggested that the presence of diabetes insipidus in patients with pineal germinomas indicates that germinomatous tissue is also present on the floor of the third ventricle despite negative neuroradiographic findings [14, 16].

Although germ cell tumors may be disseminated at the time of diagnosis, symptoms and signs of spinal cord or cerebral cortical involvement are uncommon, except for those infrequent cases of germinomas which arise in the thalamus or basal ganglionic region.

**DIAGNOSIS**

In the majority of clinical situations, biopsy of the intracranial tumor is required for specific diagnosis. Both computed tomography and magnetic resonance imaging (MRI) are highly sensitive in the detection of pineal and suprasellar masses, as well as germ cell tumors in other regions of the brain (Fig. 1) [17, 18]. Pineal calcification on skull radiographs, uncommon in children less than 10 years of age, is a useful clue to the diagnosis of a germ cell tumor, since approximately 70% of patients with pineal region tumors have calcifications [19, 20].

The neuroimaging characteristics of germinomas and nongerminomatous germ cell tumors are similar enough to limit diagnostic certainty, and either tissue confirmation or the measurement of specific tumor markers are needed for diagnosis [17, 18]. In addition, in the pineal region, germ cell tumors cannot be definitively separated on basis of neuroimaging characteristics from other tumors, such as pineoblastomas, pineocytomas, or gliomas. In the suprasellar region, germinomas may be difficult to separate from other lesions, including germinomas which infiltrate the surrounding brain mimicking gliomas and histiocytomas. In general, mixed germ cell tumors tend to be more invasive than pure germinomas. Pineal teratomas can often be differentiated based on more frequent areas of fat and large areas of calcification.

Tumor markers, as reviewed earlier, have been used to diagnose the specific type of tumor present [10]. When these markers are elevated, especially at high elevations, the diagnosis of a form of mixed germ cell tumor is essentially

---

**Figure 1. Pineal region germinoma in a 17-year-old male with anterior third ventricular extension.** Sagittal T1 weighted contrast enhanced image (A) reveals an enhancing mass occupying the pineal region, distorting the tectum. The lateral and third ventricles are markedly dilated; prominent enhancement along the anterior wall of the third ventricle represents dissemination of germinoma into the chiasmatic recess of the third ventricle (arrow). Axial CT image (B) following placement of VP shunt shows the hyperdense characteristic of the mass with a central calcification.
confirmed. Similarly, isolated high elevations of β-HCG strongly suggest the presence of a choriocarcinoma. Milder elevations of β-HCG are of less use, as they may be representative of a mixed germ cell tumor, choriocarcinoma, or possibly other forms of malignancy in the pineal region.

In the past, a frequent means to determine the histological type of pineal region tumors, without surgery, was to diagnose the tumor on the basis of its response to radiotherapy [21]. Patients with presumed germ cell tumors were given 2,000 cGy of radiation to the area of abnormality and if the tumor regressed after such treatment, a diagnosis of germinoma was made. If there was minimal or no response, biopsy was recommended. Although it is true that germinomas will respond to radiotherapy, other germ cell tumors will also respond, as will the pineoblastomas. Given the differing types of treatment required for germ cell tumors, the use of responsiveness to radiotherapy as a diagnostic tool is now frowned upon.

**STAGING**

Germ cell tumors, especially germinomas, can disseminate the neuroaxis at the time of diagnosis or early in the course of illness. There is no specific staging system which has been uniformly accepted for germ cell tumors, and most investigators utilize the TM system employed for medulloblastomas [22]. M0 are those tumors without evidence of metastatic disease as determined by post- or prediagnosis MRI of the entire brain and spine and cerebrospinal fluid cytological examination. M1 are those patients with free-floating tumor cells, which is relatively common in patients with germ cell tumors [23]. In one series, eight of nine children with germinomas, and one of two patients with malignant undifferentiated teratomas, had identifiable tumor cells in the cerebrospinal fluid and normal spinal neuroimaging finding at the time of diagnosis [23]. In another series of adult and pediatric patients, nearly 50% of patients had abnormal cytologies [24]. M2 and M3 patients are those with lump disease in the spinal region or cranial subarachnoid space.

Staging for the actual size of the tumor at the time of diagnosis or after surgery, so-called T-stage evaluation, has not been routinely employed in germ cell tumors, predominantly because of their midline location.

**MANAGEMENT: GENERAL ASPECTS**

Despite the lack of large prospective studies evaluating patients with germ cell tumors, treatment for germ cell tumors has become somewhat divergent as recommendations for treatment differ between pure germinomas and other forms of germ cell tumors [25]. Although all germ cell tumors are, to some degree, radiosensitive and most are chemosensitive, the relative roles of surgery, radiotherapy, and chemotherapy in the management of such lesions remain controversial and undecided.

In general, although there is a consensus that surgery is required in the majority of patients for diagnosis (with the exception of those with clearly characteristic marker elevations), the value of extensive surgical resections, especially total or near-total resections, is unproven [25]. Radiotherapy has been the backbone of treatment for patients with germinomas as well as nongerminomatous germ cell tumors, but there is no unanimity concerning the dose or volume of irradiation needed for any form of germ cell tumor, especially if chemotherapy is employed [1, 14, 22]. Chemotherapy has been shown to be an integral component of the treatment of testicular and ovarian germ cell tumors but has only recently been integrated into the management of intracranial germ cell tumors [1, 14, 22]. Attempts have been made to utilize chemotherapy both before and after radiation therapy, and more recently as sole treatment after surgical confirmation, for patients with intracranial germ cell tumors.

**PROGNOSIS: GENERAL ASPECTS**

The prognosis for germ cell tumors, independent of their location in the CNS, is highly dependent on the histological subtype of the tumor present [1, 26, 27]. In reported series of patients treated for germ cell tumors, it is often difficult to determine the relative prognosis of a specific type of tumor, given the variability of treatment, even at one institution. In general, germinomas carry an excellent prognosis, with most series suggesting five-year progression-free survival rates and cure in well over 90% of patients.

The syncytiotrophoblastic variant of germinoma may carry a less favorable prognosis than pure germinomas, although this has not been found to be the case in all series. In one study of 44 patients with germinomas, 20 were noted to have mild to moderately elevated β-HCG levels in the serum and cerebrospinal fluid [28]. Patients in this study were treated with radiation alone, with the majority receiving 4,000 to 4,500 cGy to the local tumor site, but the craniospinal radiation was variable. There was no difference in survival rate for those patients with or without syncytiotrophoblastic germinomas, as the overall survival rates were 100% for patients with germinomas with syncytiotrophoblastic giant cells and 89% for those with “pure” germinomas. Other series have suggested a poorer survival rate for β-HCG-secreting tumors [29]. Similarly, in some, but not all, series, suprasellar germinomas were considered to have a poorer prognosis than those lesions arising in the pineal region.

In contradistinction, nongerminomatous germ cell tumors, including mixed germ cell tumors and embryonal cell carcinomas or tumors that have been termed yolk sac tumors, have a poorer prognosis, with reported survival rates ranging
between 40% and 70% [1, 14, 26, 27]. Unfortunately, most published series lump together all forms of nongerminomatous germ cell tumors when reporting outcome. Recent reports have suggested a better outcome for nongerminomatous germ cell tumors, especially mixed germ cell tumors, with the use of more aggressive multimodality therapy [30, 31]. Most reviews contain only a small number of patients with teratomas, and reported teratomas are not always separated into mature and immature lesions. Mature teratomas seem to have a relatively favorable outcome, while immature teratomas have a less favorable prognosis with survival rates in the 50% to 70% range.

**MANAGEMENT: GERMINOMAS**

As discussed previously, the prognosis for patients with germinomas is quite good, with many series reporting survival rates of greater than 90% five years following diagnosis and treatment [1, 14, 22, 26, 27]. Interpretation of studies is somewhat difficult in that series often report a mixed group of patients, some of whom were biopsied and some of whom were treated based on neuroradiographic findings alone. In addition, there is often no mention in reports of the performance or result of staging studies for extent of disease at the time of diagnosis.

Doses of primary site irradiation in most series have ranged between 4,000 and 5,500 cGy [32-41]. Some studies have suggested poorer survival if doses lower than 4,000 cGy of radiation are delivered to the primary site [1, 40] (Table 3). Even more variation is seen in the use of cranial or spinal radiotherapy. Craniospinal radiation is almost uniformly recommended for patients with evidence of disseminated disease at the time of diagnosis. In a recent review of 40 patients, treatment with 5,200 cGy of local irradiation therapy, 3,240 cGy of whole brain irradiation therapy, and 2,600 cGy spinal radiation therapy resulted in a five-year, progression-free survival rate of 97% in patients who had evidence of leptomeningeal disease at the time of diagnosis, as long as craniospinal irradiation was given [42].

The long-term efficacy and toxicity of local whole-ventricular, cranial, or craniospinal irradiation in patients without disseminated disease at the time of diagnosis remain unclear. Some series report excellent survival rates after local radiation therapy alone, although noting that 3%-10% of patients will develop isolated leptomeningeal disease after local radiation therapy. In contradistinction, in one recent series of 48 patients, all of whom had biopsied tumors, 49% of patients who received local radiation therapy developed tumor relapse intracranially outside the primary site and/or in the spine, while no patient who received craniospinal radiation had tumor failure [40]. Conclusions are hard to draw, given the variations in patient selection and dose and volume of radiation given. However, in general, after craniospinal irradiation, especially if greater than 4,000 cGy are given to the local tumor site, most reports suggest a high rate of primary disease control. After local radiation therapy alone, which is often hard to define since some authors consider whole ventricular radiation the same as local radiation, the

### Table 3. Radiation therapy alone for germinoma (selected series)

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Tumor location</th>
<th>Local dose (cGy)</th>
<th>Whole-brain dose</th>
<th>Craniospinal dose</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wara et al. [34]</td>
<td>19</td>
<td>P or S</td>
<td>4,050-5,500</td>
<td>Variable</td>
<td>Variable</td>
<td>69%, 5-yr disease-free</td>
</tr>
<tr>
<td>Jenkin et al. [32]</td>
<td>16</td>
<td>P or S</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td>10/10 pineal alive and well (2 relapsed)</td>
</tr>
<tr>
<td>Sano et al. [8]</td>
<td>60</td>
<td>32 P; 20 S</td>
<td>5,000-6,000</td>
<td>Variable</td>
<td>Variable</td>
<td>Pineal 64.7% 5-yr (1982) survival; suprasellar 100% 5-yr survival</td>
</tr>
<tr>
<td>Shimhamoto et al. [39]</td>
<td>70</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td>84% 5-yr (1988) survival verified</td>
</tr>
<tr>
<td>Huh et al. [41]</td>
<td>32</td>
<td>14 S; 4 P; 2 P and S 12 others</td>
<td>5,400</td>
<td>3,600</td>
<td>(given up to 2,400 in 29)</td>
<td>96.9% 5-yr survival</td>
</tr>
<tr>
<td>Haddock et al. [40]</td>
<td>48</td>
<td>median 4,400 (Range 74-5,940)</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td>&gt; failure if less than 4,000 local; &gt; failure in those with local or partial whole brain</td>
</tr>
<tr>
<td>Hardenberg et al. [42]</td>
<td>40</td>
<td>11 P; 12 S; 17 midline</td>
<td>5,200</td>
<td>3,240</td>
<td>2,600 in 30</td>
<td>97% progression-free survival</td>
</tr>
</tbody>
</table>

P = Pineal; S = Sellar.
survival rates reported have been more variable, ranging from over 90% to as low as 49%.

The primary rationale for limiting the extent of radiation in patients with germinomas is to decrease the long-term sequelae of treatment. Whole brain irradiation may result in significant neurocognitive and endocrinological sequelae. Since the majority of patients with germinomas are post-pubertal at the time of diagnosis, the effects of cranial irradiation, or for that matter craniospinal irradiation, on linear growth is less than that reported in series of younger children given radiation therapy for other primary CNS tumors, such as medulloblastomas. The cognitive sequelae following craniospinal radiation in children with germinomas have not been well characterized. Studies in children receiving cranial irradiation for other types of brain tumors have suggested significant intellectual compromise secondary to such irradiation, although demonstrations of a fall in overall intelligence in older children (those greater than 10 years of age) have been hard to substantiate. Most studies suggest that older children have more difficulties in school despite relatively stable intelligent quotients. In a recent retrospective review, 22 patients treated with 3,600 cGy of craniospinal irradiation for germinomas, at a mean age of 16.9 years at diagnosis, completed a quality-of-life survey on average 10 years after successfully completing treatment [43]. All patients had completed high school, nine completed or were in college and five had advanced degrees.

Since the outcome of children with germinomas who have received localized radiation therapy alone has been variable, there have been attempts to utilize chemotherapy to decrease the dose or volume of irradiation, or, in one study, obviate the need for radiation therapy. Chemotherapy is an integral component of the treatment of testicular and ovarian germ cell tumors and a variety of different chemotherapeutical agents have been shown to have efficacy in non-CNS germ cell tumors [44-49]. The rationale for the use of chemotherapy for intracranial germ cell tumors has been either to improve survival in those patients with disseminated disease or reduce sequelae, by limiting the amount of radiation needed in patients with localized disease. In one study, cyclophosphamide alone or the drug combination of vinblastine, bleomycin, cyclophosphamide, and cisplatinum was given to 15 newly diagnosed patients with intracranial germinomas, including 7 of 11 patients with germinomas who had disseminated disease at the time of diagnosis [50]. Complete responses to chemotherapy were frequently noted in this study to either the cyclophosphamide alone or the four-drug regimen. Ten of the 11 patients in this series with germinomas had complete responses, and the dose of radiotherapy to the primary tumor site was reduced to 3,000 cGy and the craniospinal dose lowered from 3,600 cGy to 2,000 cGy in those with a complete response. Ten of these 11 patients were disease-free for a median of 47 months following diagnosis; however, it is unclear whether this rate of survival was better than what would have been seen after craniospinal radiation therapy alone. In another study, carboplatinum alone was given to four patients with multifocal germinomas [51]. Following preradiation chemotherapy with the carboplatinum, the dose to the involved area was reduced from 5,000 to 3,000 cGy and the craniospinal dose lowered from 3,600 cGy to 2,100 cGy. The survival rate was 100% using this approach in the four patients treated. In a series of 29 patients with germinomas in various regions of the brain, including pineal, suprasellar, thalamus, and bifocal lesions, treatment was undertaken with preradiation chemotherapy utilizing various drug regimens which included carboplatinum, VP-16 and ifosfamide [52]. Those patients who had an excellent response to treatment then went on to receive local radiation therapy alone, at a dose of 4,000 cGy. Four-year, event-free survival in this study was 93.3%. In another treatment trial, 17 patients with germinomas, including 11 with a syncytiotrophoblastic form of the therapy, received preradiation chemotherapy with a variety of different drugs and 2,400 cGy of local radiation therapy [53]. The authors report that 100% of these patients survived, with a two-year, progression-free survival of 94%.

In the largest series attempting to use chemotherapy alone for patients with germinomas, 45 children and adults with germinomas received carboplatinum, etoposide, and bleomycin following diagnosis [54]. Patients who had achieved a complete response after four cycles of chemotherapy received two more cycles of chemotherapy, but no radiation therapy. Despite an overall excellent response to chemotherapy, 22 of 45 germinoma patients relapsed, which is considerably higher than studies utilizing radiation therapy. Many of the patients who relapsed could be salvaged with either further chemotherapy or radiation therapy, but the two-year, overall survival for patients with germinoma was 84%.

In summary, outcome for patients with germinomas treated with craniospinal radiation therapy and local doses of radiation therapy of greater than 4,000 cGy, has been excellent. Data to unrefutably confirm the need for craniospinal radiation therapy in patients with nondisseminated disease are lacking, although the best overall disease-free progression rates have been reported in series where craniospinal radiation has been utilized. There is no consensus on what constitutes local radiation therapy and progression-free survival has been variable in series which have used more localized radiation therapy ranging from nearly 100% to as low as approximately 50% at five years. Although a variety of different chemotherapeutic agents will result in significant tumor shrinkage in patients with germinomas, it is unclear whether the addition
of chemotherapy actually improves survival. Chemotherapy may allow for a reduction in the local and/or craniospinal dose of radiation, but chemotherapy alone cannot be recommended for children with isolated or disseminated germinomas.

**Nongerminomatous Germ Cell Tumors**

The treatment of nongerminomatous germ cell tumors is unsettled, and most series lump together a variety of different nongerminomatous germ cell tumors when discussing results. There is the suggestion from one study that patients with gross total excision have an improved chance at long-term survival; however, this has not been extensively confirmed [55]. Although craniospinal radiotherapy is an essential component of the treatment for nongerminomatous germ cell tumors, it alone is rarely curative as a single treatment modality, with the majority of tumors relapsing within 18 months [1, 56]. Recent results suggest that chemotherapy can improve the overall duration and rate of survival when used in conjunction with craniospinal radiotherapy, as part of initial treatment. The most active agents include cisplatin, carboplatin, etoposide, bleomycin, ifosfamide, and vinblastine [50, 56-59]. The majority of treatment reports contain information about only a few patients, which highlights the relative rarity of these tumors and the difficulty in designing the best treatment.

The combination of carboplatin, etoposide and bleomycin was used to treat 71 patients with germ cell tumors, including 28 with nongerminomatous germ cell tumors, following surgical resection [54]. Fifty-seven percent had a complete response after four cycles of therapy, and the overall response rate was not different in the germinoma group than in patients with nongerminomatous germ cell tumors. Patients with a complete response received two more cycles of chemotherapy and no radiotherapy. Of the 55 patients that achieved a complete response to chemotherapy (and were not treated with radiotherapy), 51% relapsed at a median of 18 months from diagnosis [54].

A study of five patients with nongerminomatous germ cell tumors treated with four cycles of conventional-dose cisplatin and etoposide, followed by radiotherapy (3,000-4,000 cGy whole brain with a 1,500-2,000 cGy boost) and then additional chemotherapy, resulted in a median survival of 88 months [60]. Reduced-dose radiotherapy following cisplatin and etoposide chemotherapy was used to treat eight patients with nongerminomatous germ cell tumors, and all patients were alive and disease-free at a median of 51 months [61]. Intra-arterial chemotherapy with osmotic opening of the blood-brain barrier has been used in four patients with germ cell tumors with encouraging preliminary results [62].

In an attempt to avoid radiotherapy by using high-dose chemotherapy, six patients were treated following gross total excision of their tumor with four to seven courses of high-dose cisplatin (200 mg/M$^2$), etoposide (1,250 mg/M$^2$) and ACNU (150 mg/M$^2$), followed by autologous stem cell rescue. All patients were alive and living with good performance status one to seven years following diagnosis [63].

The future therapeutic trials for patients with nongerminomatous germ cell tumors will likely include more aggressive chemotherapy regimens with either new agents or combinations of existing agents and a reduction in the dose of consolidation craniospinal radiotherapy.

**References**

319

320 Intracranial Germ Cell Tumors


Erratum

INTRACRANIAL GERM CELL TUMORS
Roger J. Packer, Bruce H. Cohen, Kathleen Coney
The Oncologist 2000;5:312-320

Page 312 contained an error:

Kathleen Coney should read Kathleen Cooney.