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Pineal Region Tumors

JEFFREY C. ALLEN, JEFFREY BRUCE, LARRY E. KUN, AND LAUREN LANGFORD

Tumors of the pineal region can be divided into three categories (Rubinstein, 1970): *(1)* germ cell tumors, which range from surgically curable mature teratomas to the malignant germ cell tumors capable of metastasizing throughout the neuraxis; *(2)* pineal parenchymal tumors, such as the low-grade pineocytoma and the malignant pineoblastoma; and *(3)* other tumors such as intra-axial astrocytomas, ependymomas and mixed gliomas, and rare tumors of surrounding structures (meningioma, dermoid, epidermoid).

GERM CELL TUMORS

Background and Pathology

Germ cell tumors are relatively uncommon, constituting 3% to 5% of large institutional pediatric tumor series and 0.5% to 1% of adult brain tumor series (Hoffman et al., 1983). Table 7–1 summarizes the frequency of predominantly adult surgical pathology cases seen at the New York Neurologic Institute (Bruce and Stein, 1995). Germ cell tumor cases constituted 37% of their series of 160 cases. The origin of these non-neuroectodermal, primary brain tumors is unknown but may be related to an early period of ontogeny when the fetal germinal cells migrate widely throughout the body, including the central nervous system (CNS). Normally, germinal cells not residing in tissues destined to form sex organs become apoptotic and die; presumably some may occasionally survive and over many years transform into a neoplasm. The sites of origin of germ cell tumors in the CNS are unique, that is, extra-axial locations in proximity to the pineal gland and infundibulum. In unusual instances when germ cell tumors arise in the brain of infants or patients with Down's syndrome, other locations may predominate (Chik et al., 1999).

Germ cell tumors have several unique epidemiologic features such as the age at onset, sites of origin, and racial and sex predilections. The peak age at onset lies within the second and third decades of life, thereby including both the pediatric and adult populations. The primary sites of origin lie within midline extra-axial spaces such as the pineal region (45%), suprasellar region (35%), both regions (10%), and other locations (10%). Interestingly, the incidence of CNS germ cell tumors is extraordinarily high in the Japanese population, constituting 15% to 18% of primary CNS tumors in several large institutional series compared with 3% to 5% in North American reports (Jennings et al., 1985).

More than 95% of CNS germ cell tumors are biologically malignant, that is, capable of rapid growth, invasion, and metastasis. Histologically, approximately 65% of CNS germ cell tumors are pure germinomas, and most of the remaining ones are either pure nongerminomatous germ cell tumors (NGGCT) such as embryonal carcinoma, endodermal sinus or yolk sac tumor, choriocarcinoma, immature or malignant teratoma, or mixed malignant tumors. Mature teratomas that are slow growing and noninvasive are the least common variant ($<5\%$). The pure germinomas are more commonly found in the pineal region, whereas NGGCT occur more frequently in the

Table 7–1. Summary of Pathology in 154 Patients Undergoing Surgery for Pineal Region Tumors at the New York Neurological Institute

Tumor Pathology	*No.*	*Sex (M/F)*	*Mean Age (Years)*
Germ cell	57 (37%)	51/6, 89% male	20.3
Germinoma	26		
Teratoma	9		
Lipoma	2		
Epidermoid	2		
Mixed malignant germ cell	14		
Immature teratoma	2		
Embryonal cell carcinoma	2		
Pineal cell	35 (23%)	19/16, 54% male	33.7
Pineocytoma	19		
Pineoblastoma	7		
Mixed pineal	9		
Glial cell	43 (28%)	21/22, 49% male	28.9
Astrocytoma	23		
Anaplastic astrocytoma	3		
Glioblastoma	4		
Ependymoma	10		
Oligodendroglioma	2		
Choroid plexus papilloma	1		
Miscellaneous	19 (12%)	11/8, 58% male	45.7
Pineal cyst	4		
Meningioma	9		
Other malignant	3		
Other benign	3		
Totals	154	102/52, 66% male	28.9

Data are from Bruce and Stein (1995).

suprasellar region (Edwards et al., 1988; Malogolowkin et al., 1990; Rueda-Pedraza et al., 1987). There exists a male predominance (3/1 [US] to 10/1 [Japanese]) in germ cell tumor series in the pineal location, but there is an equal sex distribution or female predominance for suprasellar primary tumors (Jennings et al., 1985).

Because the management and prognosis of patients with intracranial germ cell tumors is very dependent on histology, it is imperative to establish an unequivocal diagnosis prior to the administration of radiotherapy (RT) and/or chemotherapy. For example, germinomas are readily curable with RT alone or combinations of RT and chemotherapy; NGGCT are potentially curable with maximal surgical debulking and intensive chemotherapy and RT; and teratomas are curable with surgery alone (Jennings et al., 1985).

Primary intracranial germ cell neoplasms are histologically similar to gonadal germ cell tumors. Germinoma is histologically identical to the seminoma (testes) or dysgerminoma (ovary). Germinomas are typically composed of two cell types: large, uniform polyhedral cells with clear cytoplasm that resemble primordial germ cells; and smaller lymphoid cells. The large cells contain abundant intracytoplasmic glycogen. Their round nuclei contain one or more prominent nucleoli (Fig. 7–1). Although not neces-

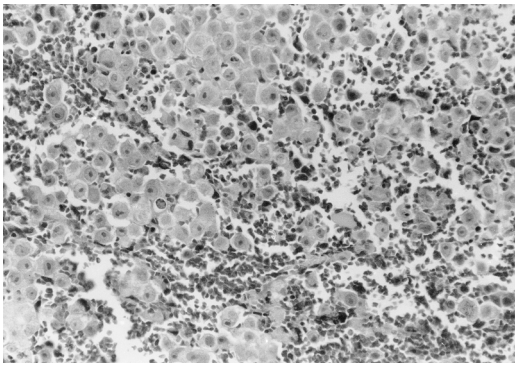

Figure 7–1. Germinomas contain large cells with clear cytoplasm and scattered lymphocytes. Hematoxylin and eosin, ×200.

sary for diagnosis, immunohistochemical studies can help in problem situations when only limited material is available. No single antigen, however, has been identified as "specific" for germinoma (Table 7–2). The lymphocytic component is immunopositive for antibodies to leukocyte common antigen, whereas the larger epithelioid cells may react to antibodies for placental alkaline phosphatase and cytokeratins (Felix and Becker, 1990). Some germinomas may also contain syncytiotrophoblastic cells, which are immunoreactive with antibodies to human β-chorionic gonadotropin.

From a treatment perspective, the malignant NGGCTs are the most challenging. Endodermal sinus tumor and choriocarcinoma resemble extra-embryonic tissues, and the embryonal carcinoma appears similar to fetal embryonal tissue. Endodermal sinus tumors (yolk sac tumor) consist of glomeruloid structures composed of a space lined by tumor cells with an invaginated vascular pedicle covered by a monolayer of the same cells. This tumor is considered to represent a neoplasm whose cells are partially differentiated into extra-embryonic structures that express yolk sac potential (Gonzalez-Crussi, 1979). Embryonal cell carcinoma is considered the most histogenetically primitive of the germ cell tumors, with features of anaplastic columnar to cuboidal cells arranged in sheets and cords (Bjornsson et al., 1985). This tumor shows a variable pattern of acinar, papillary tubular, or solid structures. A lymphocyte infiltrate may also be present but is not as abundant as in germinomas. Embryonal cell carcinoma may give rise to a multiplicity of tumor admixtures, with the most advanced form being teratoma. Choriocarcinomas are examples of differentiation along extraembryonic pathways and are composed solely of cytotrophoblastic and syncytiotrophoblastic cells without true villous formation. The primary immunohistochemical marker of this tumor is human β-chorionic gonadotropin, which is secreted by the syncytiotrophoblast; however, positive staining for human β-chorionic gonadotropin is not exclusively diagnostic of choriocarcinoma (Midgley and Pierce, 1962). Primary intracranial choriocarcinomas are rare (Bjornsson et al., 1986).

A relatively uncommon form of germ cell tumor is the pure teratoma, a tumor that is composed of mature tissues from all three germ cell layers (endoderm, mesoderm, and ectoderm). Pineal teratomas are complex mixtures of tissues that occur most frequently in males, in contrast to sacrococcygeal teratomas, which occur more often in females. Pineal teratomas are largely well differentiated or mature, but immature teratomas with malignant features do occur (Bjornsson et al., 1985). Any CNS teratoma,

Table 7–2. Tumor Marker Profile For Germ Cell Tumors

Tumor	*AFP*	*Cytokeratin*	*HCG*	*PLAP*
Germinoma			"+"	+
Choriocarcinoma		+	++	+/−
Embryonal carcinoma		+		+
Endodermal sinus tumors	++	+		+/−
Malignant teratoma	+/−	+		

+ = cases are positive; +/− = some cases are positive and some cases are negative; "+" = positive in special cases where syncytiotrophoblastic giant cells are seen; ++ = prominent immunohistochemistry appearance; AFP = α-Fetoprotein; HCG, β-chorionic gonadotropin; PLP, placental alkaline phosphatase.

however, can harbor foci of a malignant germ cell tumor; therefore, adequate sampling is of the utmost importance. If no other malignant elements are detectable, this variant can be managed with radical surgical resection alone. This strategy also pertains to other mature teratoid or embryonal tumors, such as dermoids and epidermoids.

Tumor Markers

The tumor markers α-fetoprotein (AFP), human β-chorionic gonadotropin (HCG), placental alkaline phosphatase, and lactic dehydrogenase isoenzymes are useful in the diagnosis and treatment monitoring of germ cell tumors. Elevations in levels of AFP alone in cerebrospinal fluid (CSF) and serum are found in pure endodermal sinus tumor. Elevated levels of both HCG and AFP are found in embryonal carcinoma, and high levels of HCG alone are found in choriocarcinoma. The serum and CSF levels in cells of AFP may be 10 to 100 times baseline. Serum HCG levels may be 100 times baseline, and there may be a CSF/serum gradient, especially when lumbar CSF is assayed. Modest elevations of HCG may be found in germinoma, usually in the presence of elevated placental alkaline phosphatase and/or lactic dehydrogenase isoenzymes (Allen, 1987). A serum or CSF HCG >50 IU/L and/or an AFP >25 ng/ml in the presence of a midline CNS tumor is supportive of a diagnosis of NGGCT (Calaminus et al., 1997).

Clinical Presentation

The clinical presentation of germ cell tumors varies with the site(s) of primary and/or metastatic disease. For suprasellar primary tumors, especially germinomas, the prodrome may be long, that is, from months to several years. Typically, a child may present with signs and symptoms of hypopituitarism (i.e., diabetes insipidus, growth failure, or secondary hypothyroidism) or precocious puberty. Initial neurodiagnostic studies may be noninformative. Children with acquired hypopituitarism are prime candidates to harbor germ cell tumors and should be followed expectantly with magnetic resonance imaging (MRI) scans at regular intervals. Visual field or acuity impairments and hydrocephalus occur late in the prodrome, when the tumor is large or disseminated. An MRI scan may disclose an extra-axial enhancing mass in the suprasellar and/or pineal region or intraventricular seeding in the third or lateral ventricles with hydrocephalus. A diagnostic surgical procedure is typically performed after a stress or therapeutic dose of corticosteroids is administered.

Patients with primary tumors arising in the pineal region tend to have a much shorter prodrome (i.e., weeks to several months). These patients usually present with signs and symptoms of raised intracranial pressure, such as headache, diplopia, and lethargy due to aqueductal obstruction. Tectal compression can cause Parinaud's syndrome (vertical gaze paresis, impaired pupillary light reflex, and convergence nystagmus). The MRI scan will reveal a pineal region-enhancing mass, which may protrude into the posterior region of the third ventricle with acute hydrocephalus (Fig. 7–2). Following high-dose corticosteroid therapy, the patient may need to be stabilized with ventriculostomy before definitive surgery.

General Management Considerations

The management of primary intracranial germ cell tumors is changing. Surgery is becoming an increasingly safer procedure for patients with suprasellar and pineal region tumors, and histologic documentation is a prerequisite for optimum therapy. The management of germ cell tumors is histology dependent and different protocols are emerging for patients with pure germinomas and nongerminoma germ cell tumors. During a prior era when surgical approaches to the pineal region were associated with considerable morbidity and mortality, the standard practice was to administer a therapeutic/diagnostic course of focal radiation therapy to 20 Gy. If the tumor underwent a major regression, a presumptive diagnosis of germinoma was made and the patient then received a full course (55 Gy) of focal and, in some institutions, craniospinal radiation. If the tumor did not respond to the 20 Gy dose, a diagnostic surgical procedure could be performed.

This approach is no longer favored for several reasons. Germinomas are not the most prevalent tumors in the pineal region in either pediatric or adult series, and the incidence of various tumor types is not readily predictable. For example, the incidence of germ cell tumors in the pineal region reported in two recent operative pediatric series from the Children's Hospital of Philadelphia (Packer et al., 1984) and the University of California, San Francisco (Edwards et al., 1988) were 32% and 61%, respectively. The in-

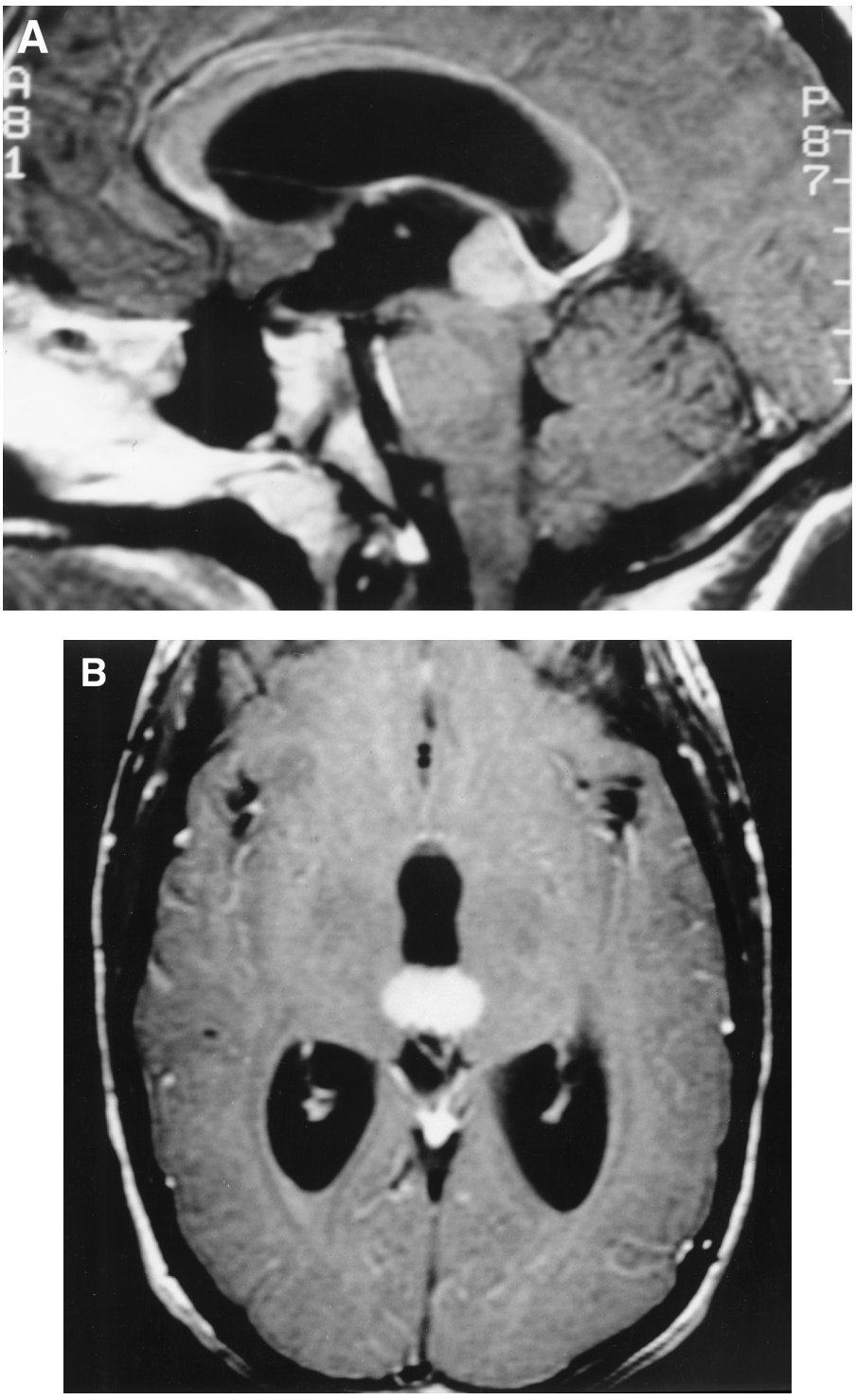

Figure 7–2. **(A)** Sagittal MRI scans with contrast of an 18-year-old man who presented with symptoms of increased intracranial pressure. The MRI shows a homogeneously enhancing pineal mass causing obstruction of the aqueduct of Sylvius. **(B)** Axial MRI of same patient. **(C)** Intraoperative photograph showing what turned out to be a germinoma. The superior colliculi are seen just inferior to the tumor. **(D)** Sagittal MRI 3 months after surgery and radiation therapy; no evidence of residual tumor is shown. (*continued*)

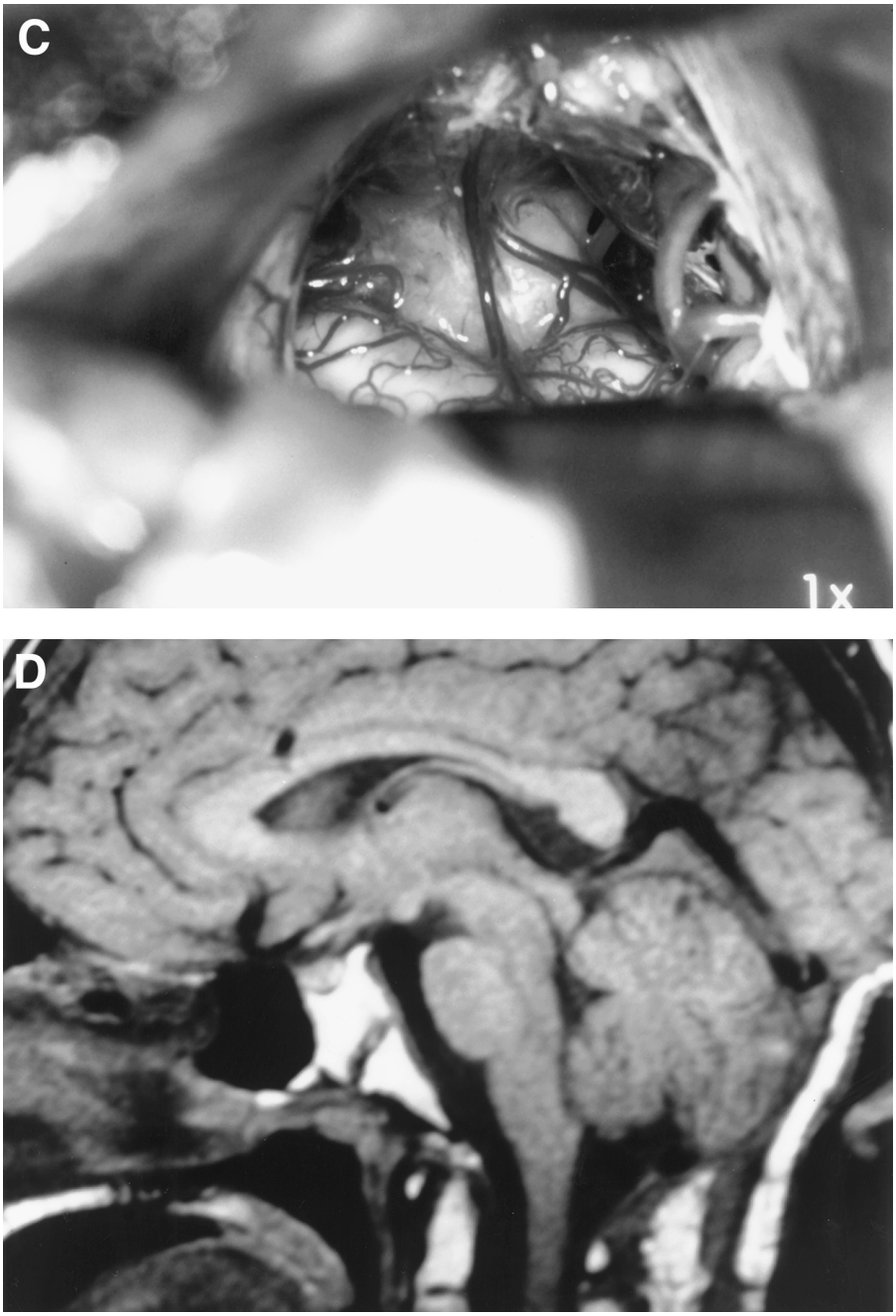

Figure 7–2. (*Continued*)

cidence in two adult series was 38% (Linggood and Chapman, 1992; Bruce and Stein, 1995). The incidence of pure germinoma in the two pediatric series was 20% (7/35) and 31% (11/36), respectively.

Other malignant tumors (pineoblastoma and malignant ependymoma) may respond to RT, but their management is quite different from that for germinoma. If a low-grade tumor such as an astrocytoma, pineocytoma, or teratoma exists, radical surgical resection alone rather than RT may be the treatment of choice. For certain tumors, such as ependymoma and malignant astrocytoma, focal RT is indicated; pi-

neoblastomas and some germ cell tumors are generally treated with craniospinal RT. Most importantly, radiographic studies cannot reliably distinguish among these tumors. Surgery not only provides important diagnostic information, but radical resection of a malignant tumor may confer a therapeutic benefit. With modern neurosurgical techniques (operating microscope, image guidance, Cavitron, and so forth), the surgical morbidity is significantly reduced.

Figure 7–2 shows preoperative (Fig. 7–2A,B) and postoperative (Fig. 7–2D) MRI images of an 18-year-old male with a germinoma who presented with a 2 to 3 week history of progressive headache, nausea and vomiting, and diplopia whose examination revealed papilledema and Parinaud's syndrome. Figure 7–2A (saggital) and Figure 7–2B (axial) reveal a homogeneously enhancing pineal region mass extending into the posterior third ventricle. Aqueductal compression caused hydrocephalus. Figure 7–2C depicts the surgeon's view of the tumor through the operating microscope, and Figure 7–2D shows an MRI that confirms a radical resection.

Following surgery, the patient should be examined for possible CNS metastases. Central nervous system tumor dissemination may be present in 10% to 30% of patients with germ cell tumors at diagnosis (Allen, 1987; Hardenbergh et al., 1997). Complete staging includes lumbar Cerebrospinal fluid examination for malignant cells and tumor markers and MRI scans (head and spine) with gadolinium enhancement. CSF examination for malignant cells may not, however, be particularly helpful immediately after a surgical procedure; the accuracy of this examination increases over time and is more reliable 2 weeks or more after surgery. Like any CSF examination for malignant cytology, a negative result does not rule out leptomeningeal dissemination. As discussed earlier, germ cell tumor markers can be used in some cases to confirm the presence of a specific germ cell component. If detectable, these markers can also be used for tracking response to therapy or tumor recurrence. Table 7–2 indicates the expected tumor marker profile for each of the histologic tumor types.

Surgical Management

Objectives

Because a wide variety of histologic tumor subtypes can occur in the pineal region, establishing a definitive diagnosis is essential. Surgical biopsy is the only method for establishing a definitive diagnosis as features seen radiographically are not a reliable predictor of histology (Tien et al., 1990). Combined advances in surgical technique, neuroanesthesia, and postoperative management have decreased morbidity and mortality rates for pineal-region surgery to acceptable levels (Edwards et al., 1988; Neuwelt et al., 1979; Stein and Bruce, 1992). The specific tumor histology has important implications for determining prognosis, staging evaluation, choice of adjuvant treatment, and optimal strategies for long-term follow up. The one exception to the requirement for tissue diagnosis in a patient with a pineal-region tumor is the detection of elevated HCG or AFP in serum or CSF on the preoperative evaluation. The role of second-look surgery is more controversial. For patients with NGGCT who may be referred to a treatment center with subtotally resected disease, rather than attempting a radical resection before adjuvant therapy, the patient should first be treated with chemotherapy with or without RT. If the markers are still elevated or there is still residual disease on MRI, second-look surgery is indicated. Surgical resection may be curative. Residual tumor usually consists of benign germ cell elements that have been more resistant to therapy, with the malignant portions having been eradicated.

Control of Hydrocephalus

Nearly all patients with pineal-region tumors present with symptomatic hydrocephalus, which often requires urgent attention, either medically or surgically. This observation is useful in distinguishing neoplastic from benign conditions such as pineal cysts, which may be found incidentally in evaluating patients who have headache disorders. For patients who do not respond to high-dose corticosteroids, a ventriculostomy or shunt may be necessary. Preoperative control of hydrocephalus is desirable, as it allows a gradual decompression of the ventricles and intracranial pressure before surgical resection. Additionally, it facilitates CSF removal for tumor marker analysis and cytologic examination.

Several methods are available for controlling hydrocephalus, each with advantages and disadvantages. Placement of a permanent ventriculoperitoneal shunt alleviates the problem by diverting CSF from the cerebral ventricles to the peritoneal cavity, and it carries a low complication rate. However, shunt malfunction, infection, and, rarely, peritoneal seeding of

malignant tumors are potential complications (Bruce and Stein, 1993). If the tumor can be removed, the patient may not need the shunt at all.

To avoid some of the drawbacks of shunts, an endoscopically guided third ventriculostomy is preferable (Goodman, 1993). By passing a small endoscope through a burr hole into the ventricles and floor of the third ventricle into the prepontine cistern, the surgeon may relieve obstructive hydrocephalus. This method avoids the risks of tumor seeding and shunt malfunction. The tumor may also be biopsied with this instrument. If a germinoma is diagnosed and the CSF markers are negative, then a craniotomy can be avoided as the patient has a medically curable disease. Major drawbacks of this method include the possibility that the ventriculostomy may close and a small risk of catastrophic hemorrhage during fenestration (Ferrer et al., 1997).

Patients who present with mild hydrocephalus and a tumor that appears resectable may be treated without any diversion of CSF. For these patients, a ventricular drain can be placed at the time of surgical resection. This drain is left in place for several days and removed when tolerated.

Optimum Methods of Obtaining Diagnostic Tissue

An open procedure, an endoscopic visually guided biopsy, and a stereotactic biopsy are the three methods available to secure tissue for diagnosis. An open procedure is nearly always preferred as it reduces the risk of sampling error. Ordinarily, a larger amount of tumor specimen will be available for histopathologic examination. This is critical not only because many pineal tumors are of mixed histology (Russell and Rubinstein, 1989; Stein and Bruce, 1992) but also because many of the histologic subtypes are rare and difficult even for experienced neuropathologists to interpret. An open operation with aggressive tumor resection is the preferred method of treatment for the one-third of pineal tumors that are benign (Stein and Bruce, 1992). Malignant tumors may also benefit from a thorough debulking to reduce the tumor burden before radiation therapy or chemotherapy (Stein and Bruce, 1992; Sano, 1976; Lapras and Patet, 1987). Surgical resection alone is sufficient treatment for some subgroups of slow-growing tumors such as pineocytomas, astrocytomas, ependymomas, and dermoids (Bruce and Stein, 1993).

Stereotactic biopsy guided by computed tomography (CT), which involves localizing a deep target lesion and passing a thin biopsy needle through it, is an alternative method for obtaining tissue (Dempsey et al., 1992). The biopsy needle secures a small core of tissue approximately 1×3 mm in size. Stereotactic biopsy can be performed relatively easily at a medical center where advanced stereotactic equipment is available. There are, however, considerable drawbacks to this procedure, the most significant being the potential for sampling error in a heterogeneous tumor or an erroneous diagnosis as only a small tissue sample is provided (Chandrasoma et al., 1989; Edwards et al., 1988). Because these are closed procedures performed by passing a probe through brain tissue, several anatomic features of pineal tumors make them undesirable for sampling by stereotactic biopsy for technical reasons. The risk of hemorrhage is heightened because of an adjacent deep venous system, the vascular nature of some malignant tumors, and their periventricular location, which allows minor bleeding to persist into the ventricle without tamponade by the surrounding tissue (Peragut et al., 1987). There have also been rare reports of implantation metastasis (Rosenfeld et al., 1990). The endoscopic biopsy procedure is attractive for patients who will undergo a third ventriculostomy and whose tumors protrude into the posterior third ventricle. The risks include limited biopsy material and hemorrhage.

Surgical Approaches to the Pineal Region

Three surgical approaches to the pineal region are used, each with advantages and disadvantages: infratentorial supracerebellar, suboccipital, and paramedian transcallosal (Bruce and Stein, 1993). The surgeon's degree of comfort and experience with the procedure play a major role in the approach chosen.

Surgical results depend more on the tumor's invasiveness and relationship with surrounding structures than on which approach is utilized. The deep location of these tumors makes surgery risky. An infratentorial approach is favored because it allows the most direct access to these midline tumors and, if a sitting position is used, allows gravity to work in the surgeon's favor when dissecting the tumor from the surrounding deep venous system. Supratentorial approaches are best suited for large tumors that have a significant lateral or supratentorial component.

Supratentorial approaches have the disadvantage of requiring brain retraction or sacrifice of bridging veins, which can lead to focal neurologic deficits.

Surgical Results

Most large surgical series reported by experienced neurosurgeons using microsurgical techniques report morbidity rates ranging from 0% to 12% and mortality rates ranging from 0% to 8% (Bruce and Stein, 1993). The largest series cited a mortality rate of 4% and a major morbidity rate of 3% (Stein and Bruce, 1992). Most series involving stereotactic biopsy demonstrated minimum mortality and morbidity; however, some errors in diagnosis occurred (Bruce and Stein, 1993). The most common operative-related complications involve extraocular movement dysfunction related to tectal trauma (Bruce and Stein, 1993). Altered mental status and ataxia can occur, but generally these deficits are temporary. Many of these problems are present preoperatively as a result of tumor compression and hydrocephalus and thus make it difficult to distinguish preoperative from postoperative morbidity. Ultimately, most complications are transient and improve with time. Shunt malfunction is another frequent complication (Bruce and Stein, 1993).

Multimodality Treatment Considerations

Much recent interest has been aroused concerning the application of adjuvant RT and/or chemotherapy following the diagnosis of a malignant germ cell tumor. Most clinical investigators use different treatment strategies for the management of germinomas and nongerminoma germ cell tumors such as endodermal sinus tumors, choriocarcinomas, embryonal carcinomas, and immature teratomas. Germinomas are readily curable with high-dose RT alone or with combinations of moderate-dose chemotherapy and RT, and the major concern is to minimize the late effects of therapy. NGGCTs are less responsive to therapy, and the goal is to improve survival by intensification of treatment.

Radiotherapy

Radiation has been the primary curative treatment for germinomas arising in the pineal and suprasellar regions. Durable disease control rates in excess of 65% to 90% are well documented in the literature (Linstadt et al., 1988; Legido et al., 1989; Dearnaley et al., 1990; Jenkin et al., 1990; Fuller et al., 1994). However, this survival rate is achieved at a high price as the late effects of RT on cognitive and neuroendocrine function may be significant. In addition, many medical centers also employ craniospinal RT (36 Gy) regardless of whether CNS metastases are present, and this therapy has additional late effects on spinal growth and cognition. Although responsive to irradiation, other malignant germ cell tumors such as endodermal sinus tumors, embryonal carcinomas, or choriocarcinomas in pure or mixed form are controlled in fewer than 10% to 25% of cases involving RT alone (Jennings et al., 1985; Dearnaley et al., 1990; Linggood and Chapman, 1992; Fuller et al., 1994).

The appropriate therapeutic radiation volume for pineal and suprasellar germinomas remains highly controversial. Recommendations vary from irradiation of limited local fields to coverage of the third ventricle, the entire ventricular system, the full cranium, or the entire neuraxis (craniospinal irradiation). The incidence of neuraxis dissemination is estimated at 10% to 20% in pineal germinomas and at 10% to 35% in suprasellar germinomas (Sung et al., 1978; Rich et al., 1985; Linstadt et al., 1988; Dearnaley et al., 1990; Jenkin et al., 1990; Fuller et al., 1994). A suggestion that biopsy predisposes to subarachnoid seeding, especially in lesions of the pineal region, is difficult to confirm, as benign tumor types may confuse outcome data among cases not undergoing biopsy (Linstadt et al., 1988; Dearnaley et al., 1990; Fuller et al., 1994). The excellent disease control and limited toxic effects following low-dose craniospinal irradiation in prepubertal patients favors administering craniospinal irradiation to 25 to 30 Gy followed by a local "boost" to the tumor site for a total of 50 Gy (Hardenbergh et al., 1997). Lower doses to the neuraxis may also be effective. A European pilot study (MAKEI 89) involving 49 germinoma patients reduced the craniospinal dose to 15 Gy while administering 45 Gy to the primary tumor. The 5 year progression-free survival in this series was 91% (Bamberg et al., 1999). A retrospective review of the Mayo Clinic experience involving 48 patients treated between 1935 and 1993 indicated that the spinal axis failure rate in patients who received partial brain volumes at 5 years from diagnosis was 49% compared

with 0% for patients who received whole-brain or craniospinal treatment (Haddock et al., 1997).

Despite the obvious radiosensitivity of these tumors, dose–response data clearly indicate the necessity to deliver 50 Gy or more to the primary site. The "boost" encompasses the entire third ventricle for those with multiple midline germinomas, a relatively frequent adolescent presentation marked by two or more lesions around the midline structure (Rich et al., 1985; Dearnaley et al., 1990; Jenkin et al., 1990). There is little controversy that craniospinal irradiation is necessary in the few cases with neuraxis dissemination at diagnosis. Numerous recent series, however, question the necessity to treat beyond the local or third ventricular volume, as disease control rates in excess of 75% to 90% have been reported with more limited radiation volumes (Linstadt et al., 1988; Glanzmann and Seelentag, 1989; Dattoli and Newall, 1990; Fuller et al., 1994).

The majority opinion regarding treatment of both pineal and suprasellar germinomas appears to support wide local irradiation that includes the primary tumor with or without the adjacent third ventricle. This approach extrapolates to the 10% to 25% of adolescent males who present with multiple midline germinomas, which are believed to represent independent primary tumors or subependymal extension rather than subarachnoid seeding (Linstadt et al., 1988; Fuller et al., 1994). Some radiotherapists favor continued use of low-dose craniospinal irradiation for postpubertal patients based on a small but discernible benefit balanced against very limited added morbidity; for young children or patients who elect more limited treatment, wide local radiation fields can certainly be justified.

For the NGGCT types, an inferior survival rate with RT alone and the higher incidence of neuraxis recurrence supports the coordinated use of chemotherapy and craniospinal irradiation to near-tolerance levels (approximately 35 to 40 Gy) (Dearnaley et al., 1990; Allen, 1991; Fuller et al., 1994).

Chemotherapy

Chemotherapy is being utilized with increasing enthusiasm for both germinoma and nongerminoma germ cell tumors. For germinomas, attempts have been made to reduce or defer RT after a trial of neoadjuvant chemotherapy. In one study, following surgical confirmation of a pure germinoma and determination of the extent of CNS disease, two courses of high-dose cyclophosphamide were administered (Allen et al., 1987). A complete response (CR) or disappearance of all measurable disease was observed in 10 of 11 patients, and these 10 then received a 33% reduction in RT dose. The radiation volume (focal versus craniospinal) was determined by the extent of disease at diagnosis. Patients with localized disease at diagnosis who had a CR received involved-field RT only (30 Gy); those with disseminated disease received craniospinal therapy (24 Gy) plus a boost to the primary tumor. After a median of 5 years follow-up, only one patient developed a recurrence.

In an attempt to lower the risk of infertility after cyclophosphamide chemotherapy, the neoadjuvant chemotherapy has been changed to single-agent carboplatin. To date, the results of this trial show seven objective responses (six complete and one partial response) in eight patients with evaluative disease. The dose of RT was reduced in five patients who achieved a CR with carboplatin alone (Allen et al., 1994).

Pre-RT multidrug regimens have also been used with modifications of dose and volume of RT in attempts to lessen the late effects of RT. In a French study of 47 patients with germinoma, four courses of neoadjuvant chemotherapy (etoposide/carboplatin alternating with etoposide/ifosfamide) were administered before RT (40 Gy for localized disease). The 3-year, progression-free survival was 96% (Bouffet et al., 1999). Multidrug therapy with agents such as cisplatin and etoposide has also been used with encouraging results in a neoadjuvant setting with reduced-dose RT at the Mayo Clinic in a smaller pilot study of nine patients with germinoma (Buckner et al., 1999).

One study attempted to achieve long-term remission with chemotherapy alone. A multinational protocol developed at Memorial Sloan-Kettering Cancer Center administered six courses of carboplatin, etoposide, and bleomycin to 45 patients with germinoma and 26 with NGGCT. For those patients not experiencing a CR, two further courses of cyclophosphamide were administered. If a CR was achieved, RT was deferred. Although a CR was achieved in 78%, permitting a deferral of RT, 49% recurred after a median of 13 months of follow up. Most of these patients were salvaged with additional chemotherapy and high-dose RT (Balmaceda et al., 1996). These experiences support the continued use of multimodality therapy for newly diagnosed germinoma patients.

Based on these observations, multi-institutional and cooperative studies are underway to optimize pre-radiation chemotherapy and lower radiation doses and field sizes. Siffert and colleagues (2000) reported an ongoing study of patients with newly diagnosed germinoma who were treated with two courses of carboplatin and etoposide; if a CR was achieved they received reduced doses (typically 30.6 Gy) of radiation therapy and a reduced field if one site was involved. Patients who failed to achieve CR received two additional courses of cisplatin and cyclophosphamide before radiation therapy. This approach appears promising as 18 of 19 patients achieved a chemotherapy-induced CR with carboplatin and etoposide and reduced-dose radiation therapy.

Much progress has been made in the management of patients with NGGCT. A pilot multi-institutional study based at NYU Medical Center treated 18 NGGCT patients with a multimodality regimen employing chemotherapy (cisplatin/etoposide), RT, and then chemotherapy (bleomycin, vinblastine, carboplatin, and etoposide). The 4 year progression-free survival rate was 67% (Robertson et al., 1997). Another German/Italian pilot study treated 19 NGGCT patients with neoadjuvant chemotherapy (cisplatin/etoposide/ifosfamide) followed by RT. Preliminary results revealed an 81% progression-free survival rate at 12 months (Calaminus et al., 1997). Attempts to use single-modality therapy with either RT alone (Jennings et al., 1985) or chemotherapy alone (Balmaceda et al., 1996) produced an unacceptably high recurrence rate. Twelve of 13 patients in a French pilot study relapsed following 6 cycles of multiagent chemotherapy alone and deferral of RT (Baranzelli et al., 1998). Patients with NGGCT have a most favorable prognosis with combinations of chemotherapy, RT, and radical surgical resection either at diagnosis or for residual post-treatment disease.

Management of Recurrence

Because of the rarity of pineal tumors, standard regimens for their treatment at recurrence do not exist. Treatment decisions for recurrences should consider histologic diagnosis, previous response to treatment, and the time to recurrence. A second operation is useful for patients with slow-growing tumors of low malignancy. Chemotherapy, either conventional or high dose with stem cell support, can be useful for patients with recurrent malignant germ cell or pineal cell tumors, although their prognosis is poor. Radiosurgery (especially multiple-day fractions) is an attractive option for patients with localized tumor recurrences less than 3 cm in diameter. Fractionated conventional external-beam radiation is rarely a therapeutic option for recurrences, as it is generally given to its maximum allowable dose at initial tumor presentation. Patients with either germinomas or NGGCTs who have relapsed following chemotherapy alone can, however, be salvaged with multimodality therapy (Merchant et al., 1998; Baranzelli et al., 1998).

PINEOCYTOMA/PINEOBLASTOMA

Pathology

Neoplasms arising from pinealocytes or pineal parenchyma are rare. Traditionally these tumors have been categorized by grade as pineocytomas (low grade) and pineoblastomas (high grade) (Schild et al., 1993; Herrick and Rubinstein, 1979; D'Andrea et al., 1987). Pineocytomas occur in adolescence or adulthood. They are circumscribed, noninvasive, and slow growing. Histologically they resemble the normal pineal gland (Fig. 7–3).

Pineoblastomas are high-grade tumors resembling medulloblastomas in appearance and behavior. Morphologically they are composed of primitive, small cells that frequently form neuroblastic rosettes (Fig. 7–4). Pineoblastomas, in contrast to pineocytomas, have a propensity to seed the subarachnoid space.

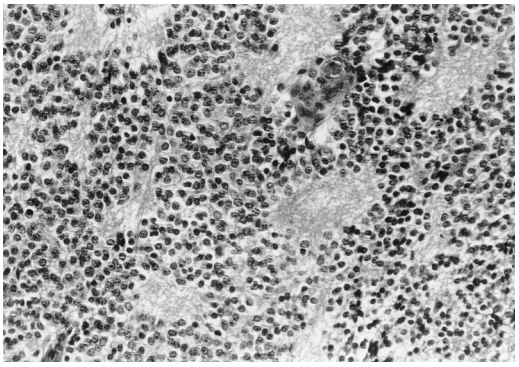

Figure 7–3. Pineocytomas have round nuclei and fibrillary cytoplasm compartmentalized into lobules. Hematoxylin and eosin, ×200.

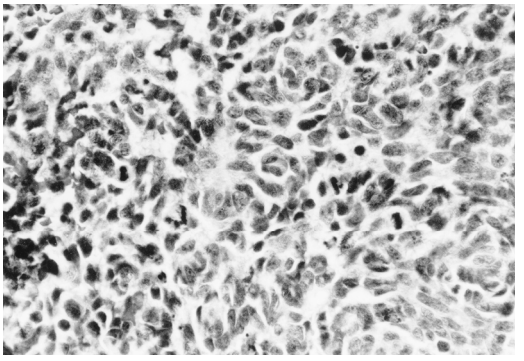

Figure 7–4. The primitive cells in a pineoblastoma have high nuclear/cytoplasmic ratios resembling neuroblastomas and medulloblastomas. Hematoxylin and eosin, ×200.

Clinical Presentation

In a population-based study from Manitoba, Canada (1980–1989), comprising all ages, pineal parenchymal tumors accounted for 1% of 315 cases (Sutherland et al., 1987). Pineal parenchymal tumors constituted 3.4% (8/234) of tumors in a large institutional survey of pediatric brain tumors in the Children's Hospital of Philadelphia series. Three pineocytomas and five pineoblastomas together comprised 32% (8/25) of the pineal region tumors from the same pediatric series (Packer et al., 1984). The incidence of pineal parenchymal tumors in a large, predominantly adult, series of 154 patients from the New York Neurologic Institute at Columbia University was 17% (Bruce and Stein, 1995).

Pineal parenchymal tumors present in a fashion similar to germ cell tumors with predominant symptoms related to aqueductal obstruction (raised intracranial pressure) and midbrain compression (Parinaud's syndrome). The malignant pineal parenchymal tumors (pineoblastoma or primitive neuroectodermal tumor) tend to arise in children with a median age of onset of 5 years (Packer et al., 1984). Pineocytomas arise predominantly in adults. The median age of onset of pineocytoma in an adult necropsy series of five cases was 51 years (Borit et al., 1980). The average duration of symptoms was 4 years.

Management

Because of the rarity of pineal parenchymal tumors, controversy surrounds their management. Pineocytomas in adults are, for the most part, locally aggressive and infrequently metastasize; optimum management consists of maximal surgical resection with or without involved-field RT. These tumors resemble an intraventricular neurocytoma, a relatively benign neuronal tumor that can be managed with radical surgical resection alone. Pineocytoma diagnosed in a child is problematic. Although the histologic diagnosis implies a relatively favorable prognosis, there have been a number of case reports of children with pineocytomas developing widespread CNS metastases (D'Andrea et al., 1987). Of six Children's Hospital of Philadelphia patients with pineocytomas, five received craniospinal RT and two received chemotherapy. Median progression-free survival rate was 2 years, and three patients died (D'Andrea et al., 1987). In an adult series, the median survival was 7 years, and at necropsy all had died of localized disease without evidence of metastases (Borit et al., 1980). Thus, pineocytomas may behave differently in adults than in children.

Pineoblastomas are managed in a similar fashion to primitive neuroectodermal tumors elsewhere in the CNS. Their prognosis relates, in part, to the same prognostic variables that govern the management of medulloblastoma. Standard-risk patients include those with gross total resections who have no metastases at diagnosis. High-risk patients consist of those with any of the following criteria: minimal resections, positive CSF cytology (M-1), diffuse leptomeningeal metastasis (M-2 or M-3), and diagnosis made when the patient is younger than 3 years. Infants and children under 3 years of age tend to be treated according to infant brain tumor protocols with intensive chemotherapy alone. Overall, they have a poor prognosis. In the Childrens Cancer Group protocol 921, eight infants younger than 2 years of age at diagnosis with pineoblastoma were treated only with the "8 drugs in 1 day" protocol. Under this schedule, all infants developed progressive disease and died. The median progression-free survival rate was 4 months (Jakacki et al., 1995), and this chemotherapy regimen was judged to be ineffective.

For children old enough to receive RT, multimodality therapy (surgery, RT, and chemotherapy) appears to be the preferred method. Chemotherapy may be given before and/or following RT, as in Childrens Cancer Group protocol—local; 36 Gy—craniospinal. Any measurable CNS metastases identified during the staging evaluation received additional RT. Results of a relatively large Childrens Cancer Group

series (15 patients) treated on this randomized protocol are more favorable, with a 3-year progression-free survival rate of 61% (Jakacki et al., 1995). It is difficult to obtain comparative survival data from other large studies. Most prior publications are case reports, and patients were managed in a variety of ways (i.e., involved-field RT, craniospinal RT, and RT plus chemotherapy). Craniospinal RT appears to be the most effective treatment to date, and the added benefit of adjuvant chemotherapy can only be surmised from data concerning medulloblastoma clinical trials.

ASTROCYTOMAS

Astrocytomas are discussed briefly because they are one of the most common pineal region tumors. Astrocytomas are not pineal parenchymal tumors but arise in adjacent regions of the thalamus or midbrain. They are managed similarly to those arising elsewhere in the CNS, except they are more surgically inaccessible. Treatment guidelines are based on histologic grading. Because radical resections are difficult to perform in this region, the prognosis for high-grade fibrillary astrocytomas of the pineal region is poorer than the already dismal prognosis for high-grade astrocytomas elsewhere in the brain. The prognosis of low-grade astrocytomas is variable. The diffuse low-grade fibrillary astrocytoma behaves similarly to a brain stem glioma with a 3 year survival of less than 5% (Reardon et al., 1998). Low-grade juvenile pilocytic astrocytomas have a more favorable outcome. One variant, the tectal or midbrain glioma, appears to have a protracted course and may be managed with ventriculoperitoneal shunt and deferral of surgery or RT (Squires et al., 1994). For children or adults with radiographic and clinical progression from a midbrain or thalamic juvenile pilocytic astrocytoma, chemotherapy or RT may produce long-term palliation (Packer et al., 1993; Petronio et al., 1991).

CONCLUSIONS

It is clear that patients with symptomatic pineal region tumors benefit from a surgical procedure to establish a histologic diagnosis and control raised intracranial pressure. Modern multimodality therapy for these uncommon malignant tumors should involve participation in cooperative group clinical trials.

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