Management of Pineal Region Tumors

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Opinion statement

Tumors of the pineal region represent a diverse collection of tumors with a variety of natural histories. This diversity necessitates accurate histologic diagnosis to allow rational therapeutic planning. Evaluation of a pineal lesion should begin with craniospinal MRI and analysis of the cerebrospinal fluid (CSF). Whereas certainty of the histologic diagnosis is now a requirement for treatment in Western nations, some Asian centers continue to recommend a test dose of radiation therapy based on the high incidence of germinoma in those countries. If there is high clinical suspicion of a germinoma or tectal glioma, stereotactic or endoscopic biopsy may be pursued. All other lesions should be referred for open biopsy with microsurgical techniques. This approach provides adequate tissue for diagnosis, may be curative in low-grade tumors, and may substantially improve survival in patients with malignant tumors. If open surgery is not desired by the patient or practitioner, stereotactic or endoscopic biopsy may be followed by radiosurgery for localized, well-demarcated tumors. Radiation therapy is the first-line therapy for germinomas. Although the optimal radiation dosage and volume have not been decided, the current Children's Oncology Group trial may offer definitive evidence to address this dilemma in germ cell tumors. Evidence of CSF seeding requires craniospinal radiation and adjuvant chemotherapy regardless of tumor type. Diagnosis of any of the malignant tumors (non–germ cell tumors, pineoblastomas, and parenchymal tumors of intermediate determination) also requires craniospinal radiation (with local tumor doses of at least 50 Gy) and adjuvant chemotherapy (generally platinum based). Patients with tectal gliomas may undergo excision with or without postoperative radiation; however, they also may be observed with vigilant follow-up alone.

Introduction

A diverse collection of tumors are found in the pineal region and generally reflect the cell types normally present there (Table 1). The region is anatomically located posteriorly in the midline between the roof of the third ventricle dorsally and the tectum of the midbrain caudally (Fig. 1). The pineal gland itself is an endocrine gland responsible for the synthesis and secretion of melatonin in response to light–dark cycles. It arises from the roof of the third ventricle, sits between the superior colliculi of the midbrain, and is covered by the pia mater. It is composed predominantly of pinealocytes, which give rise to pineocytomas and pineoblastomas. Gliomas in the pineal region may develop from a small population of astrocytes within the pineal gland or from glial cells in the base of the thalamus or midbrain. Germ cell tumors (GCTs) arise from primitive embryonal cells and have a predilection for the pineal region. Meningiomas (arising from the pia encasing the pineal gland and making up the velum interpositum lining the third ventricle), choroid plexus papillomas, and ependymomas from the third ventricle also occur in this area. Rarely, metastases, lymphomas, or neuronal tumors may present in the pineal region.

Pineal region tumors account for 1% to 3% of all primary brain tumors. They affect all age groups, but are roughly 10 times more common in children than in adults, accounting for 3% to 11% of childhood brain tumors [1••]. All tumors in this region present similarly because of the involvement of neighboring brain structures. The most common presentation is headache, nausea, vomiting, and dizziness due to compression of the aqueduct of Sylvius, resulting in obstructive hydrocephalus and elevated intracranial pressure. Less common presentations include ocular and vision abnormalities consistent with Parinaud syndrome (light-near dissociation, convergence/retraction nystagmus, and vertical gaze palsy) secondary to dorsal midbrain compression. Rarely, there may be focal weakness or cranial nerve symptoms. Initial evaluation includes MRI of the brain and spine and analysis of cerebrospinal fluid (CSF) tumor markers.

OVERVIEW: PINEAL REGION TUMOR TYPES

Germ cell tumors GCTs are thought to arise from primordial germ cells residual from embryogenesis. They are the most common pineal region tumor (accounting for 31% to 85% of all pineal region tumors) but involve other regions of the brain, including the third ventricle, suprasellar cistern, thalamus, and basal ganglia [1••,2–4]. The histologic subtypes include germinoma, teratoma, embryonal carcinoma, yolk sac tumors, and choriocarcinoma. Mixed GCTs have multiple subtypes, and the prognosis is determined by the most malignant component [3]. The subtypes are divided into germinomatous (germinoma) and nongerminomatous (NGCTs; the remaining types) based on their natural histories. Germinomas are exquisitely sensitive to radiation and have the best prognosis. Mature teratomas may also be cured if complete resection is possible; all other NGCTs have very poor prognoses.

GCTs present most commonly in adolescence and appear to affect males more frequently than females [4,5]. Germinomas are the most common of the GCTs, followed by mixed GCTs and teratomas. Interestingly, both mediastinal and intracranial GCTs may be associated with Klinefelter syndrome (47XYY), particularly when children present with precocious puberty [6,7]. There are regional differences in the incidence of GCTs. In Asian countries, GCTs are more common overall (accounting for 3% of all primary brain tumors) but are predominantly the more benign germinomas [4,8]. In Western countries, GCTs are less common overall (0.3% to 0.5% of all primary brain tumors) but are more likely to include NGCTs.

Both germinomas and NGCTs may seed throughout the CSF; therefore, craniospinal MRI and CSF studies are required both at the time of diagnosis and periodically after treatment for surveillance. All GCTs appear similar on imaging, with the most common characteristic being calcification of the pineal gland. The few distinctive imaging features are presented in Table 2. The most important CSF parameters for these tumors are the tumor markers human chorionic gonadotropin (βHCG) and α-fetoprotein (αFP). CSF βHCG is significantly elevated in choriocarcinoma. αFP is a sensitive marker of yolk sac and embryonic tumors [8]. Although βHCG may be mildly elevated in some germinomas, significant elevations in CSF βHCG and/or αFP are diagnostic of NGCT. In general, higher elevations are associated with more aggressive tumors and worse prognoses [2]. βHCG and αFP are also found in the serum, but the CSF βHCG and αFP are far more sensitive measures of disease, and these studies are required in the diagnosis and surveillance of GCTs.

The prognosis of GCTs is widely variable and depends on the histologic subtype. Germinomas have

Table 1. Pineal region tumors

Germ cell tumors
Germinomatous
Germinoma
Nongerminomatous
Teratoma (mature and immature)
Embryonal carcinoma
Yolk sac tumors
Choriocarcinoma
Pineal parenchymal tumors
Pineocytoma
Pineoblastoma
Pineal parenchymal tumor of intermediate determination
Gliomas
Tectal glioma
Thalamic glioma
Pineal glioma
Meningioma
Ependymoma
Metastases, lymphoma, neuronal tumors

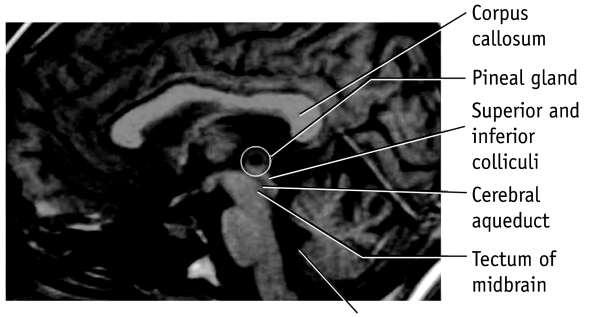

Figure 1. MRI T1-weighted image of a pineal region cyst to demonstrate anatomy of the pineal region.

Table 2. Unique imaging features of pineal region tumors

Tumor	Distinct imaging features
Germinoma	Hyperdense on CT, mildly hypointense on T1, mildly hyperintense on T2; "butterfly": calcified pineal gland centrally with symmetric "wings" of tumor [1••]
Teratoma	Very heterogeneous signal characteristics due to fat, cysts, and calcification
Choriocarcinoma	Intense contrast enhancement, calcification, high propensity for intratumoral hemorrhage
Pineocytoma	Slightly increased signal intensity on FLAIR and T2-weighted images; likely to have a cystic component [13]

FLAIR—fluid-attenuated inversion recovery.

the most favorable prognosis as they are exquisitely radiosensitive and can be cured with radiotherapy alone: the 5-year survival rate is 65% to 100% [1••,3]. However, there are cases of metastatic germinomas after local control, hence vigilant long-term follow-up is required. Mature teratomas can be cured if complete surgical resection is achieved. Immature teratoma, embryonal carcinoma, yolk sac tumors, and choriocarcinoma are associated with the worst prognosis, with 5-year survival rates in the range of 9% to 49% even with aggressive therapy [8,9•,10].

Pineal parenchymal tumors Pineal parenchymal tumors (PPTs) include pineocytomas, pineoblastomas, and pineal parenchymal tumors of intermediate determination (PPTID). These tumors account for less than 1% of primary brain tumors and roughly 10% to 30% of pineal region tumors [1••,4]. Age at presentation is more variable for these tumors, ranging from 10 to 65 years [4,11•] Overall, PPTs are more common in children, and there does not appear to be a gender preference. When PPTs present in adulthood, they are more likely to be the more benign pineocytoma than the malignant pineoblastoma [11•,12••]. It is difficult to distinguish the various forms of PPT on MRI; however, signal intensity may be slightly higher with pineocytoma than with pineoblastoma on fluid-attenuated inversion-recovery and T2-weighted sequences, and pineocytoma is more likely to have a cystic component [13]. Pineocytoma accounts for roughly 30% to 60% of PPTs and may present in both children and adults [1••,4,9•]. It is slow-growing and does not appear to be invasive. The 5-year survival rate is roughly 80% to 90% with resection or radiotherapy [9•,14,15••]. Like germinomas, pineocytomas may recur with distant metastases after local tumor control, requiring long-term vigilant follow-up with MRI of the neuroaxis.

In contrast, pineoblastoma is a World Health Organization grade IV tumor associated with an overall 5-year survival of 10% to 51% [12••,14]. Without treatment, survival is on the order of months. These tumors are histologically and clinically similar to other primitive neuroectodermal tumors (PNETs), such as medulloblastoma and retinoblastoma, and mutations of the *RB1* gene (the gene associated with retinoblastoma) have been linked to more aggressive forms of pineoblastoma [16]. Like other PNET tumor types, pineoblastoma presents more commonly and carries a worse prognosis in young children [12••]. The mean age at presentation is 12.5 years, with the majority of patients younger than 10 years [17]. Some studies have observed a higher frequency of disease in females [14]; however, this has not been confirmed [15••,18]. As pineoblastoma is associated with frequent tumor shedding into CSF (14% to 43% of cases), craniospinal radiation and adjuvant chemotherapy are the standard of care. Lumbar puncture and MRI of the neuroaxis are required at the time of diagnosis and in surveillance [12••,14,18]. Pineoblastoma may also metastasize extracranially, with bone being the most common site of metastasis [19]. PPTID are generally closer in behavior and prognosis to pineoblastomas than to pineocytomas, with 165-month median survival [12••]; hence, these tumors are generally treated similarly to pineoblastomas.

Pineal region gliomas Gliomas in the pineal region most commonly arise from the dorsal midbrain and are referred to as tectal gliomas. Tectal gliomas are a distinct form of brainstem glioma in both adults and children. Regardless of age of presentation, tectal gliomas appear to have a benign course [20]. On MRI, they appear as exophytic masses that extend from the quadrigeminal plate into the periaqueductal area with variable contrast enhancement. The significance of contrast enhancement is unclear. In some series, contrast enhancement is correlated with high-grade histology [20]; however, other authors found that benign-behaving tumors often have contrast enhancement [21,22]. Recent series have shown an equal distribution between low- and high-grade gliomas in this region [20,22,23]. Some authors suggest that high-grade histology portends a worse prognosis, consistent with supratentorial gliomas [20]. Indeed, a review of the few cases of pineal region glioblastoma multiforme in the literature (roughly 19) shows survival ranging from 2 to 11 months [24]. However, other series report good long-term outcomes for all histologic subtypes [23].

Pontine brainstem gliomas arise in the pons of the brainstem remote from the pineal region. Although pontine gliomas are outside the scope of this article, it is important to be aware of these gliomas as they are far more common than tectal gliomas and have

a dismal survival rate of less than 10% at 2 years. They are most common in children and are the leading cause of death secondary to brain tumors in this population [25]. Pontine gliomas also occur in adults and appear to be more aggressive in the elderly population [20].

Treatment

Surgical considerations

- Surgery involving the pineal region was previously associated with high procedural mortality rates of 20% to 70% [15••]; therefore, biopsies or resections were rarely performed. Instead, pineal region lesions were given a trial dose of radiation without histologic diagnosis. If the lesion responded, it was presumed to be a germinoma and treated with a full course of radiation. If there was no clinical improvement, other modalities were offered. Imaging, surgical techniques, neuroanesthesia, and postoperative care all have improved dramatically in the past two decades, resulting in perioperative mortality rates of less than 5% [1••,15••]. Simultaneously, modern studies have shown that there is great heterogeneity of tumor type in this region and that optimal therapy depends on tumor histology [26]. These developments have made tissue diagnosis the standard of care [4]. That said, some experts in Asian countries (where germinomas account for up to 90% of pineal region tumors) still advocate empiric radiotherapy [2,27].
- The main goals of surgery are histologic diagnosis, CSF diversion for hydrocephalus, and, when feasible, total resection of benign lesions. The optimal surgical technique depends on the type of tumor, the overall health of the patient, and the experience of the surgeon. Maximal surgical resection may result in cure of low-grade tumors and substantially improve outcome in patients with malignant tumors. In addition, open microsurgical techniques allow maximal tissue sampling, increasing the odds of accurate histologic diagnosis. Proponents of stereotactic biopsy argue that it is less invasive, with fewer complications; however, diagnostic failures are reported 1% to 8% of the time with this approach [1••,28]. Even when a histologic diagnosis is achieved, doubt remains over whether cell types of mixed tumors have been missed because of limited sampling. Furthermore, stereotactic biopsy carries significant risk of both symptomatic and nonsymptomatic hemorrhage (up to 21%) because of the vascular nature of these tumors, the density of vascular structures in the pineal region, and the minimal surrounding structural support to tamponade bleeding [29]. Endoscopic approaches are gaining support as a minimally invasive technique for simultaneous tumor sampling and CSF diversion. As in stereotactic approaches, tissue samples may be inconclusive and there is risk of hemorrhage given the reduced ability to control bleeding with this approach [15••]. However, endoscopy does allow direct visualization, thereby mediating these limitations, and some experts argue that it should be the initial treatment for all symptomatic pineal region tumors because it can provide immediate relief of ventricular obstruction, yields tissue samples, and is well tolerated by unstable patients [30,31].

Germ cell tumors

- Tissue is desirable to confirm diagnosis of GCTs; however, there is no additional survival benefit with maximal surgical resection of germinomas because of their sensitivity to radiotherapy. Because NGCTs are diagnosed by CSF tumor markers 15% to 75% of the time [8,31,32•], surgery is generally reserved for removal of residual mass after initial therapy (chemoradiation). This so-called second-look strategy is both diagnostic and therapeutic. If

residual malignant cells are seen, additional chemotherapy is required. When malignant cells are absent, maximal resection may provide local control. This approach has resulted in survival rates of up to 90% at a mean of 96 months for NGCTs [15••,33].

Pineal parenchymal tumors

- Open microsurgery is particularly beneficial for PPTs. These tumors often have mixed histologies [11•]; therefore, adequate sampling of these tumors is crucial. Pineocytomas can be cured with radical resection (with or without adjuvant radiotherapy), and surgery is first-line therapy for these tumors. Pineoblastomas should be treated with maximal resection followed by chemotherapy and radiotherapy. The 5-year survival rate for patients with all forms of PPT who underwent maximal surgical resection was 70% versus 30% in patients who had partial resection or biopsy [1••]. In adult patients with malignant PPT, 10-year survival after treatment was 100% for those without residual disease, compared with 40% for those with minor residual disease and 15% for those with major residual disease [12••]. The greatest predictors of survival in adult patients with pineoblastoma were degree of resection and whether the patient received radiotherapy [18]. Although striking, these findings must be interpreted with caution as they are from a retrospective analysis of published cases and likely reflect both selection and publication biases.

Gliomas

- There is no consensus regarding the optimal surgical approach for pineal region gliomas. Some experts advocate observation with surgery only as needed for hydrocephalus if the tumor is small, is localized to the tectal region, and does not have contrast enhancement [34,35]. This strategy was first introduced in pediatric patients with focal tectal lesions without contrast enhancement but has recently been applied with good outcome in adults [22,35]. In a series of 10 pediatric patients with tectal tumors, the median progression-free survival was 6.5 years with hydrocephalus management alone [22]. Other authors advocate surgical resection of the tumor followed by radiation as definitive therapy [1••,20,23]. Stereotactic-guided biopsy is an option in cases of widely infiltrative tumor when histologic diagnosis is desired, but meaningful resection is not possible.

Other pineal region tumors

- Surgery is the treatment of choice for the rarest pineal tumors, such as ependymoma and meningioma. In the case of meningioma, surgery provides definitive therapy; in the case of ependymoma, it is the critical first step in multimodality therapy, with the degree of resection being a main prognostic factor for survival [36].

Management of hydrocephalus

- Between 58% and 90% of patients with pineal region tumors require CSF-diverting procedures to relieve hydrocephalus secondary to compression of the aqueduct of Sylvius [1••,37]; however, controversy persists regarding the optimal procedure. Ventricular shunting is the more definitive approach; however, it is associated with complications such as shunt failure, infections, intracranial hypotension, subdural hematomas, and in rare reports,

peritoneal metastases [22,38]. There is growing support for third ventriculostomies via neuroendoscopy, a procedure that is less invasive and has fewer complications [15••,39]. In addition, fenestrations can be made simultaneously in tumor-related cysts, allowing for tissue and fluid sampling [40]. However, ventriculostomy often requires later revision or shunt placement [22,37,40]. An important point is that small ventricular spaces hamper tumor debulking [1••]; therefore, it is best to defer CSF diversion until tumor debulking is planned. If emergent shunting is required, programmable or temporary externalized shunts should be used so that ventricular size can be manipulated during debulking.

Radiation therapy

- Although the need for tissue diagnosis is now emphasized, radiation therapy continues to play a major role in the treatment of all pineal region tumors. The major controversies involve the optimal volume of treatment (tumor vs whole brain vs craniospinal) and optimal dosing. Craniospinal radiotherapy has been the standard of care for most pineal region tumors; however, concern about sequelae such as cognitive deficits, endocrinopathies, secondary malignancies, growth arrest, and marrow suppression has led to investigation of alternative treatment strategies [41]. The risk for these morbidities is particularly high in young children and in patients with long life expectancies.

Germ cell tumors

- Radiation is the treatment of choice for germinomas. Germinomas are exquisitely radiosensitive, with 5-year survival rates of roughly 90% with radiotherapy alone [1••,4,42]. However, great debate remains over the optimal dose and volume of radiation. There were no significant differences in relapse rates when reduced-dose radiation (30–40 Gy vs 50-Gy standard dose) was used [3]. In 24 patients with germinoma, there were no significant differences between those who were treated with local, whole-brain, or whole-ventricle craniospinal radiation [42]; however, controversy regarding the optimal treatment strategy persists. Because 2% to 37% of germinomas have distant metastases after apparent local cures, some authors favor upfront craniospinal radiotherapy [28,41,43]. Others feel these low rates of dissemination do not justify the risks associated with craniospinal radiotherapy (particularly in young children) and it should be reserved for cases in which there is evidence of dissemination [1••,15••,40,42]. These concerns have led to the investigation of whole-ventricle radiation therapy with local tumor boost, radiosurgery with and without chemotherapy, and chemotherapy alone [42,44,45•]. Chemotherapy alone results in upfront complete response but has an overall survival rate of 84% at 2 years [44]; therefore, some form of radiotherapy is still required. Combined chemoradiation is playing an increasingly important role, allowing patients who respond to initial chemotherapy to receive subsequent reduced-dose radiation therapy [46•]. The current recommendations for germinoma are postoperative whole-ventricle radiation therapy (20–30 Gy), local tumor boost (50 Gy), and reservation of craniospinal radiation for patients with evidence of dissemination. However, an ongoing phase III Children's Oncology Group (COG) trial comparing standard radiation therapy versus chemotherapy followed by reduced-dose radiation will provide important data that may change the standard of care.

- NGCTs are far less radiosensitive; however, radiation is still an important part of multimodality therapy for these tumors. Overall, the doses are higher (50–55 Gy) because of the insensitivity of NGCTs to radiation. Upfront craniospinal radiation is used because of the higher rates of CSF seeding and overall poorer prognosis [1••,2,42].

Primary parenchymal tumors

- Pineocytomas are generally benign tumors that can be cured with surgical resection [15••]. However, reports of metastases from pineocytomas have led some to recommend craniospinal radiotherapy for all patients with PPTs [47]. Review of several small series suggests that there is no significant benefit to postoperative radiotherapy (in any form) for pineocytoma patients, with all patients having good long-term outcomes regardless of radiotherapy [14,40]. If postoperative radiotherapy is offered for pineocytoma, it should be local radiation only, unless there is evidence of tumor dissemination.
- In contrast, it is standard of care to treat pineoblastoma and PPTID with upfront craniospinal radiation [12••,14,18,48]. This therapy is followed by adjuvant chemotherapy in virtually all cases. Craniospinal radiation appears to prevent distant metastases and increase disease-free survival [14,49]. However, the desire to prevent the side effects associated with craniospinal radiation in very young children has led some experts to pursue alternative approaches. Efforts to delay radiotherapy using upfront chemotherapy (cyclophosphamide, vincristine, cisplatinum, and etoposide) in infants with pineoblastoma had dismal results, with all 11 patients progressing on chemotherapy and subsequently failing salvage radiotherapy [50]. Because of the desire to avoid long-term radiation-related neurologic injury on one hand and the evidence of treatment failure without radiation therapy on the other, controversy persists regarding the optimal approach for very young patients with pineoblastoma. In older children and adults, craniospinal radiation with adjuvant chemotherapy is recommended for pineoblastoma and PPTID.

Gliomas

- As the long-term outcome in patients with pure tectal gliomas is excellent without any intervention, radiation therapy should be reserved for patients who have gliomas that invade beyond the tectum or who are symptomatic. In these cases, focal radiation and chemotherapy regimens useful for parenchymal gliomas are appropriate. Controversy surrounds optimal treatment for progression or recurrence of tectal gliomas. Radiographic growth is not always associated with clinical symptoms, and some authors argue that continued close observation is reasonable, especially in pediatric patients [21,51]. Most experts recommend treatment with local radiation, radiosurgery, or chemotherapy in the setting of progressing or recurrent tectal glioma.

Radiosurgery

- Stereotactic radiosurgery via gamma knife is the most common form of radiosurgery. This technique delivers large single-fraction radiation doses to a focal area. It is generally used as part of a "minimally invasive" treatment paradigm including stereotactic biopsy [2]. The published series evaluating stereotactic radiosurgery are small and include both benign and malignant tumors, adult and pediatric patients, and variable combinations of other

treatments; hence, it is not possible to comment on its efficacy for each tumor type. Overall, the "benign" tumors (germinoma and pineocytoma) have the best outcomes [9•,27]. There may be some efficacy in local control in more aggressive tumors as well; however, additional therapies are always required for these tumors [5,9•,10].

- Stereotactic placement of interstitial radiotherapy with iodine-125 is used even more rarely for pineal region tumors. Given the very few patients treated with this approach, it is not possible to comment on efficacy at this time. However, it appears to be well tolerated and may be a useful adjuvant therapy in some cases [12••,28].

Chemotherapy

- Chemotherapy is an important part of multimodality therapy for the aggressive pineal region tumors and is playing an increasingly important role in possibly reducing the dose and/or volume of radiation.

Germ cell tumors

- Radiotherapy remains the current standard of care for GCTs. However, concerns about the long-term sequelae of radiation therapy in children have inspired trials investigating chemoradiation. In GCT, platinum-based therapy has been the most widely used regimen based on the success of these drugs in systemic GCT [32•]. Although these agents are generally not soluble across the blood-brain barrier, in the setting of ongoing disruption due to tumor, surgery, and radiation, there may be increased drug delivery to the tumor [3,45•]. Early efforts using chemotherapy alone with regimens including carboplatin or cisplatin, etoposide, and bleomycin resulted in complete response in 58% to 100% of GCTs across three series (72 patients) [44,52,53]. However, survival at 2 years was only 88% for germinomas and 48% for NCGTs [52]. More recently, etoposide (100 mg/m^2/d) and cisplatin (20 mg/m^2/d) followed by radiation (local or craniospinal; dose adjusted based on chemotherapy response) resulted in 100% survival at 4.3 years [45•]. The aforementioned trials included patients with both germinomatous and nongerminomatous tumors, which may have biased the results because of the favorable prognosis of germinomas. In patients with confirmed germinoma, carboplatin at 150 mg/m^2 weekly (4 weeks on/2 weeks off) upfront with late radiation dosed depending on response to chemotherapy in pediatric patients allowed 64% of the patients to get reduced-dose radiation (30 Gy local disease, 21 Gy craniospinal axis), with 91% in continuous remission at 25 months [54]. As mentioned, new data about the optimal approach for GCT will come from the ongoing COG trial.
- The goal of chemotherapy in NGCT is quite different. For these tumors, neoadjuvant chemotherapy is used in combination with maximal surgical resection and radiotherapy. Again, platinum-based therapies are widely used. Matsutani [8] gave carboplatin/cisplatin-based regimens with radiation (either before or after chemotherapy) to patients with various GCTs assigned good, intermediate, or poor prognoses. At a median follow-up of 3 years, remission rates were 92%, 68%, and 22%, respectively. In the prospective MAKEI89 trial, 30 patients with NGCT were given either BEP (bleomycin, etoposide, cisplatin) or VIP (vinblastine, ifosfamide, cisplatin) for two courses followed by craniospinal radiation (30 Gy) with a tumor boost dose (20 Gy) [32•]. Twenty-six of the patients (63%) also underwent surgical resection (13 total, 10 subtotal, three partial). The mean survival was 112 months (range, 50–154 months). Survival benefit was shown for

craniospinal radiation and for cisplatin given in doses of 400 mg/m^2 or greater. In a prospective trial investigating platin-based regimens as first-line therapy in patients with confirmed NGCT, 70% of patients were alive at the median follow-up of 6.3 years [55]. It is worth noting, however, that several of the subjects received radiation therapy off protocol.

- In patients with recurrent or progressive GCT (germinoma and NGCT), 78% of germinoma patients were alive at a median of 48 months and 33% of NGCT patients were alive at a median of 33 months after thiotepa-based high-dose chemotherapy (HDC) regimens with autologous stem-cell rescue (CTE [carboplatin, thiotepa, etoposide], TE [thiotepa, etoposide], TT [thiotepa, autologous stem cell rescue, thiotepa], and CTTemo [carboplatin, thiotepa, temozolomide]) [56]. Of course, this aggressive regimen was associated with multiple adverse events, including severe myelosupression, pulmonary disease, mucositis, and nausea and vomiting. Hence, the current treatment of NGCT is cisplatin-based chemotherapy and craniospinal radiation (with local tumor doses of at least 50 Gy) with subsequent resection of residual tumor [15••,32•]. The role of HDC regimens with stem cell rescue is still under investigation.

Parenchymal pineal tumors

- Although chemotherapy plays a central role in the treatment of PPTs, especially for pineoblastomas, the optimal regimen or timing of chemotherapy is unknown [14]. The regimens that have been used include single-agent cyclophosphamide or methotrexate and multiagent regimens including two to eight drugs, such as VP16, etoposide, cisplatinum, carboplatin, vincristine, and vinblastine [12••,14]. As in GCTs, platinum-based therapies may have the best efficacy [57].
- Recent studies have focused on the use of HDC in the form of various combinations of cyclophosphamide, melphalan, and busulfan followed by autologous stem cell rescue [58,59]. Four of seven pineoblastoma patients (57%) in a series of pediatric patients with recurrent malignant tumors responded to HDC and autologous stem cell rescue [57]. Gururangan et al. [59] reported even more promising results, with nine of 12 patients with pineoblastoma (75%) achieving a median survival of 62 months. As mentioned previously, upfront chemotherapy with delayed radiation in infants with pineoblastoma had a 100% treatment failure [50]; therefore, current treatment of PPT requires surgery, radiation, and adjuvant chemotherapy. There is no evidence of any single agent being optimal for these tumors.

Gliomas

- Chemotherapeutic agents used for gliomas elsewhere in the brain, including temozolomide, CCNU (lomustine), and BCNU (carmustine), also may be tried in pineal region gliomas. Given the rarity of tectal gliomas, there are no reliable data about the efficacy of these regimens in these tumors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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