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Optic Nerve, Chiasmal, and Hypothalamic Tumors

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Gliomas are the most common tumors in the optic nerve, chiasmal, and hypothalamic regions of the central nervous system (CNS). As such, they are the focus of this chapter. For completeness, the less common tumors of these regions—meningiomas and craniopharyngiomas—are also covered. Germ cell tumors can also occur in this region but are discussed in Chapter 7.

GLIOMAS

Gliomas that affect the optic nerves, chiasm, and hypothalamus represent a unique type of tumor with a variable clinical course. Histologically, most other midline astrocytomas of childhood are of the pilocytic subtype. These gliomas are among the neoplasms of the nervous system whose tumor type and prognosis are age related. Except for infants, the prognosis for patients with these tumors is inversely related to age at onset, with older individuals having a poorer prognosis. In infancy, tumors affecting the optic pathways can be malignant in their course, although the reasons for this are not known. Gliomas of the optic nerves and chiasm are strongly associated with neurofibromatosis type 1. Several large series report obvious signs of neurofibromatosis in as many as 54% of affected children (Alvord and Lofton, 1988; Hoyt and Baghdassarian, 1969; Listernick et al., 1988; Packer et al., 1983; Manera et al., 1994). Gliomas affecting the hypothalamus and anterior third ventricle are also strongly associated with neurofibromatosis and may be found in tuberous sclerosis, another hereditary condition.

The pathology of optic pathway gliomas runs the gamut from very benign astrocytomas, considered by some to be hamartomas, to tumors that are glioblastoma multiforme. The typical histologic picture of a glioma of the optic nerve is one of dense arachnoid proliferation around an infiltrating pilocytic glioma, with thin hair-like tumor cells intermixed among the fibers of the optic nerve itself. The low-grade gliomas that tend to affect the optic chiasm, anterior third ventricle, and hypothalamus frequently are characterized as juvenile pilocytic astrocytomas, having few mitoses, no malignant features, or degenerative changes such as Rosenthal fibers. Despite their relatively "benign" histology, these tumors can progress and cause considerable morbidity in young children. Occasionally, anterior third ventricle tumors are discovered in conjunction with tuberous sclerosis; these tumors are generally noninfiltrating, relatively benign subependymal giant cell astrocytoma (see Chapter 3). Overall, approximately 4% to 5% of optic pathway tumors are frankly malignant, and those usually have many of the characteristics typical of glioblastoma multiforme. The tumors with malignant histology occur most commonly in adolescents and older individuals.

In addition to patient age, anatomic distinctions are extremely important in the evolution and prognosis of these tumors. Optic nerve gliomas can be conveniently grouped into two major categories: the

anterior optic nerve glioma, which primarily affects the optic nerve or nerves; and the posterior optic nerve glioma, usually centered in the optic chiasm. Obviously, tumors in both categories affect the visual system, but the two types differ in pace and progression. Anterior optic nerve gliomas, which usually occur in childhood, are ordinarily quite benign and progress very slowly. Some of these tumors do not progress at all or progress over many years. Posterior optic nerve gliomas, which occur in very young children or older individuals, tend to form larger masses and present with more symptoms. These tumors may become large enough to affect the physiology of the hypothalamus and/or obstruct the anterior third ventricle, producing hydrocephalus. In infants who present with optic nerve or chiasmal gliomas, the spectrum ranges from indolent tumors to aggressive tumors that can spread throughout the optic pathway from the globe back to the occipital cortex.

Tumors arising primarily in the hypothalamus or anterior third ventricle are less common and less often associated with neurofibromatosis. Hamartomatous lesions also occur in the hypothalamus and in the interpeduncular fossa. More typical juvenile astrocytomas can occur in this region, along with standard anaplastic astrocytomas and other malignant forms.

Clinical Presentation

Optic gliomas occur primarily in children, with more than 71% diagnosed in patients younger than 10 years of age and 90% diagnosed during the first two decades of life (Dutton, 1991). The tumors can range from mild fusiform enlargement of the optic nerve or nerves within the orbit to very large, globular exophytic masses that extend from the chiasm and are virtually indistinguishable from a primary hypothalamic tumor.

In one series, more than 60% of optic pathway tumors involved the optic chiasm (Tenny et al., 1982). The signs and symptoms in children with optic pathway tumors who presented to The University of Texas M. D. Anderson Cancer Center between 1975 and 1993 are listed in Table 5–1 (Manera et al., 1994). The clinical picture of a patient with a lesion affecting the optic nerves, chiasm, or hypothalamus is usually one of progressive visual loss. In unilateral optic nerve tumors, this begins as a unilateral loss of optic nerve function; in other tumors, mixed variants of optic nerve and chiasmal patterns of visual loss can occur, with an asymmetric bitemporal hemianopsia being the most common finding in a chiasmal glioma.

In addition, behavioral changes, possibly related to elevated intracranial pressure or hypothalamic involvement, are prominent. Irritability, depression, social withdrawal, somnolence, and aggressive behavior have been reported. Because of the frequent involvement of the suprasellar-hypothalamic region, children with optic nerve tumors of these areas can also present with endocrine abnormalities. Although endocrine manifestations can occur with any of the suprasellar lesions, such presentations are particularly common in lesions that arise in the hypothalamus or floor of the third ventricle. The hypothalamic dysfunction produced by these lesions can range from varying forms and degrees of hypopituitarism to endocrine-active syndromes produced by tumors that secrete hypothalamic-releasing factors. Tumors that affect the physiology of the appropriate nuclei in the hypothalamus or of the pituitary stalk can result in diabetes insipidus. Finally, hypothalamic hamartomas that present in the interpeduncular fossa are also associated with precocious puberty. In a report of 33 children with optic chiasmatic-hypothalamic tumors, 5 (14%) of 33 presented with symptoms of endocrine dysfunction and 14 (56%) of 25 demonstrated endocrine abnormalities on laboratory evaluation. Growth hormone deficiency was the most common abnormality, followed by precocious puberty, delayed puberty, and diabetes insipidus. In addition, 7 (21%) of 33 patients failed to thrive and had the diencephalic syndrome (Rodriguez et al., 1990), which is characterized by severe emaciation and an inability to gain weight even when caloric intake is adequate (Russell, 1951).

Evaluations of endocrine function in children with diencephalic syndrome usually reveal normal thyroid function and elevated levels of cortisol and growth hormone. Usually the child is young at the time of diagnosis and frequently has been subjected to extensive failure-to-thrive evaluations before the diagnosis is made. Because the only neurologic findings on examination may be decreased visual acuity, visual field cuts, optic atrophy, or nystagmus, which are difficult to evaluate in a child younger than 3 years, these signs may be overlooked in a less than thorough examination.

The association of optic nerve gliomas with neurofibromatosis is well known. Optic nerve gliomas ac-

Table 5–1. Optic Pathway/Hypothalamic Tumors Referred to the Pediatric Brain Tumor Clinic at The University of Texas M. D. Anderson Cancer Center, 1980 to 1993*

	No.	%
Demographics		
Total	60	100
Neurofibromatosis (NF)	31	54
Male	34	57
Female	26	43
Symptoms at diagnosis		
Decreased visual acuity or blindness	28	47
Visual field deficit	12	20
Nausea/vomiting	17	46
Headache	19	32
Failure to thrive and diencephalic syndrome	6	10
Behavioral problems (irritability, social withdrawal, somnolence, aggressive behavior)	12	20
No symptoms with NF	12	7
Endocrine complaints	4	7
Radiographic findings		
Multilobular suprasellar-optic chiasmal masses	35	58
Optic nerve and chiasmal swelling	17	32
Isolated optic nerve	6	10
Hydrocephalus	23	38

*Median age at diagnosis was 5.2 (range, 0.75 to 14.3) years.

count for only 4% to 8% of all brain tumors in childhood (Pollock, 1994), but as many as 70% of the optic nerve glioma cases are found in individuals with neurofibromatosis type 1 (Stern et al., 1979). In a prospective study of children referred to a neurofibromatosis clinic who had no specific ocular complaints, 15% were found to have optic nerve gliomas, 30% unilateral, 30% bilateral, and 40% involving the optic chiasm (Listernick et al., 1989). In addition, all children who had plexiform neurofibromas of the eyelid and glaucoma were found through comprehensive neuroimaging to have optic nerve gliomas. Whether the natural history of these tumors in children with neurofibromatosis is the same or different from the rest of the population remains controversial.

Prognosis and Natural History

The natural history of optic pathway tumors has been debated for nearly a century, with some early investigators (Hoyt and Baghdassarian, 1969) believing that these tumors are not neoplasms, but rather are hamartomas that do not grow continuously. From the literature, however, it is clear that the clinical course of optic pathway tumors can be quite variable, ranging from rare reports of spontaneous tumor regression (Brzowski et al., 1992), to tumors that remain stable for life, as suggested by Hoyt and Baghdassarian (1969), to aggressive tumors that over time carry considerable risk of visual loss and death (Alvord and Lofton, 1988). Several factors have now been identified that at diagnosis predict favorable and poor outcomes (Kanamori et al., 1985). Table 5–2 summarizes these factors.

Most investigators have divided optic pathway tumors into two groups: anterior optic nerve gliomas with isolated optic nerve enlargement and posterior optic nerve gliomas with optic chiasmal involvement. Ten to 20 year survival rates are excellent (approximately 90%) for patients with optic nerve tumors (Weiss et al., 1987) and more variable (40%

Table 5–2. Classification of Optic Glioma by Factors Influencing Prognosis

	FAVORABLE PROGNOSIS
Age at onset	Early childhood to adolescence
Clinical features	Visual loss with laterality
	Slowly progressive or arrested course
	Incidental finding in child with neurofibromatosis
	No symptoms of endocrine dysfunction or hydrocephalus
	Does not have diencephalic syndrome
Radiographic features	Intrinsic optic nerve and/or chiasmal location
	POOR PROGNOSIS
Age at onset	Infancy to early childhood and adulthood
Clinical feature	Hypothalamic symptoms and/or signs of increased intracranial pressure
	Severely affected vision in both eyes
Radiographic features	Large exophytic chiasmal tumor with posterior extension
	Extension into third ventricle
	Hydrocephalus

Adapted from Kanamori et al. (1985) and Alvord and Lofton (1988).

to 90%) for those with optic chiasmal tumors (Packer et al., 1983; Pierce et al., 1990; Horwich and Bloom, 1985; Tao et al., 1997). Upon careful examination, it can be observed that chiasmal involvement that is not extensive and not associated with a large exophytic mass may also carry an excellent prognosis. The characteristics of tumors with the worst prognosis include early onset in infancy, hypothalamic symptoms, signs of hydrocephalus, presence of diencephalic syndrome, third ventricular involvement, and large chiasmal tumors extending posteriorly. It is most difficult to determine the best treatment for young children with these characteristics because aggressive treatment with surgery and irradiation do not necessarily lead to the best survival rates or the best quality of life (Jannoun and Bloom, 1990).

In evaluating the effects of the tumor itself and the treatment of optic chiasmal gliomas, the series from San Francisco (Hoyt and Baghdassarian, 1969; Imes and Hoyt, 1986) is useful because of its long-term follow-up period and its evaluation of the actual causes of death. In the original 1969 report, 8 of 28 patients were dead, and at follow up 15 years later 8 more had died, leaving only 12 (46%) of 28 surviving at a median follow up of 20 years. Nine of the 16 deaths occurred in patients with neurofibromatosis; only two of these patients had died of their chiasmal tumors. The remaining died of other malignant gliomas of the brain, neurofibrosarcomas of peripheral nerves, or complications of management of cervical neurofibromas. Of the seven who died without neurofibromatosis, five died as a result of tumor and three died of unrelated medical illnesses. Of those patients treated with radiation, 4 of 14 patients died because of their tumor, whereas only 5 of 14 who did not receive radiation died, 1 from tumor and 4 from other causes.

On the basis of these data, no benefit from radiotherapy (RT) could be demonstrated. In addition, the risk of death from tumor was greatest in the early follow-up period. However, most other investigators have concluded that RT does improve survival and does prolong the interval before disease progression (Alvord and Lofton, 1988; Pierce et al., 1990; Horwich and Bloom, 1985; Tao et al., 1997). For example, in a series of 26 children with chiasmal gliomas treated with RT at the Joint Center for Radiation Therapy, 60% had objective tumor shrinkage that occurred gradually over a period of 5 years. Vision either improved or stabilized in 72.7% of the children. The 15 year overall survival rate was 85.1% and freedom from progression was 82.1%, with median follow up of 108 months (Tao et al., 1997).

Management of Optic Gliomas

The literature abounds with inconsistencies, controversy, and disparate conclusions about the prognosis, natural history, and management of optic pathway gliomas. Although only 4% to 8% of childhood brain tumors originate from the optic tract, the potential morbidity of these tumors and their treatment in the face of good survival rates has resulted in extensive literature about the best forms of treatment to optimize cure rates and minimize morbidity. However, because of the relative infrequency of occurrence of these tumors and their heterogeneous behavior related to patient age and tumor location and size, most series have not reported numbers adequate to allow definitive conclusions about this relatively rare subgroup of gliomas, and randomized trials could not be conducted with them. Furthermore, as Sutton et al. (1995) aptly stated, "It is unlikely that any single modality (surgery, RT, or chemotherapy) will be the optimum treatment for all children with hypothalamic/chiasmatic astrocytoma. The challenge for the future is to determine the most appropriate treatment for each patient, based on rate of tumor progression, age, radiographic demonstration of extension of tumor, prior therapy, and visual/endocrine status." It is therefore extremely difficult to arrive at any "standard recommended treatment" for these tumors. Recognizing that controversies exist, we have adapted the following guidelines for the evaluation, treatment, and follow up of children with optic pathway gliomas.

Diagnosis

The evaluation of patients with optic pathway gliomas involves a thorough family history, an accurate assessment of visual status, evaluation for signs and symptoms of increased intracranial pressure, and delineation of the patient's endocrine status, looking for both hypopituitarism and endocrine-active syndromes. Physical examination should be directed toward these points, noting the presence of papilledema or optic atrophy, deficiencies in visual acuity or visual fields, and the general intellectual and neurologic state of the patient. Careful attention should be paid to growth and development parameters and to the presence of any lesions suggestive of neurofibromatosis or tuberous sclerosis. For asymptomatic children with neurofibromatosis with no previous diagnosis of optic glioma, routine screening with imaging or visual evoked potentials is not warranted, and tests should be determined by findings on clinical examination (Gutmann et al., 1997).

Diagnostic evaluation consists of appropriate laboratory testing, including measurement of pertinent pituitary hormones, a formal visual examination and measurement of acuity and visual fields, and imaging diagnosis, which currently rests on magnetic resonance imaging (MRI) with gadolinium enhancement for the most accurate delineation of the lesions involved.

In children with neurofibromatosis and optic nerve enlargement, characteristic findings on MRI or computed tomography (CT) scans are adequate to allow diagnosis. Unless there is a history of acute visual loss or neurologic changes, these such patients can be evaluated and followed up for objective evidence of progression. The baseline and follow-up evaluations should include complete physical and neurologic examination, careful ophthalmologic examination, including visual fields and MRI, or CT scan evaluations. The MRI scan is superior to the CT scan for detecting change, relationship of tumor to the optic chiasm, and tumor extension into adjacent brain. Visual evoked potentials can be useful if the baseline value is normal and can be very sensitive in detecting disease progression. Once vision is impaired, however, we have not found the visual evoked potentials to be very useful, especially when visual field defects are present. Unfortunately, for young, uncooperative children the visual evoked potential studies were not as useful as we had hoped. For very young children, the most useful evaluation of vision appears to be that performed by a child neurologist or pediatric ophthalmologist.

At diagnosis, it is often unclear from the patient's history how rapidly visual change is occurring; therefore, for the first 6 months to 1 year, we perform radiographic and physical examinations every 3 months. If no change is observed, evaluation intervals can be safely decreased to yearly. For children without neurofibromatosis, these guidelines can also be followed in cases of isolated optic nerve enlargement. When tumor progression is identified, options for further treatment include surgery, radiation, and chemotherapy. The pros and cons of these approaches are discussed separately.

Surgery

When a suprasellar mass is present at diagnosis, surgical resection or biopsy is usually recommended.

The extent of resection depends on the extent and location of the tumor. A biopsy is necessary to confirm the diagnosis in patients who present with a suprasellar-hypothalamic mass. Frequently, the origin of the tumor cannot be determined by radiography, and craniopharyngiomas may be indistinguishable from suprasellar germinomas. Because management of these two entities differs somewhat, a definitive diagnosis is needed.

In addition, careful surgical removal from the chiasm of the portion of the tumor that is exophytic can sometimes improve vision by relieving external pressure on the adjacent optic nerve (Oakes, 1990). Sometimes surgical debulking can also relieve hydrocephalus. These goals must, however, be balanced against the risks of increased visual loss and increased postoperative hypothalamic dysfunction, which can result in a disturbed sleep–wake cycle, distorted appetite and thirst, hyperactivity, memory dysfunction, and panhypopituitarism.

The indication for surgery varies with the type and location of the tumors affecting the optic pathways. For the typical unilateral optic nerve glioma located within the orbit, the indication for surgery is progressive visual loss and progressive proptosis. Surgery is generally the treatment of choice when there is loss of vision in an eye without extension of tumor into the chiasm. Surgical excision of the lesion when it has not reached the optic chiasm can be curative, but the eye remains blind. Current surgical techniques allow for preservation of the globe and a good cosmetic result. Patients known to have optic nerve gliomas with little proptosis and preserved functional vision can be evaluated with periodic imaging studies and visual assessments. If there is any evidence of the tumor extending toward the optic chiasm, treatment should be planned early. When surgery is indicated, the operation involves a frontal craniotomy and unroofing of the orbit, sectioning of the optic nerve at its junction with the globe, and removal of the optic nerve, including its intracanalicular segment up to its junction with the optic chiasm. Results are excellent provided that the tumor is totally excised and the remaining optic nerve is free of disease.

Astrocytomas that involve the optic chiasm cannot be resected without causing significant visual impairment. Unfortunately, the characteristics of this type of tumor, as shown by neuroimaging scans, are still not specific enough to allow a histologic diagnosis without biopsy. In these cases, the goal is to perform a safe but effective biopsy of the lesion without producing additional visual impairment. This is ordinarily accomplished with a frontotemporal type of craniotomy using microsurgical techniques for the tumor biopsy. Some tumors in this region are large enough so that the exophytic component extending from the chiasm produces obstructive hydrocephalus; in such cases, a tumor debulking that preserves the portion involving the optic chiasm can be accomplished to relieve the ventricular obstruction. This procedure can be performed accurately and safely using careful microsurgical techniques. There are reports of very satisfactory results of removal of some hypothalamic hamartomas using similar techniques, with reversal of some of the endocrine deficits, particularly precocious puberty.

Despite the risks, several neurosurgical groups have advocated radical resection as primary treatment for children with hypothalamic gliomas. Wisoff et al. (1990) reported a series of 16 children with chiasmatic-hypothalamic tumors treated with radical resection, with 11 of 16 "alive and well" 4 months to 4.5 years after surgery, most without other therapy. Infants were most likely to progress after surgery and require other therapy. It is evident that significant surgical judgment and skill are necessary to deal with these difficult lesions, as the dysfunction produced by overzealous resections can have serious, life-threatening consequences, such as memory loss, inappropriate thirst, and severe diabetes insipidus, which can ultimately result in an individual's requiring constant care. In addition, of 11 children with diencephalic syndrome after surgical intervention in an M. D. Anderson Cancer Center series (Manera et al., 1994), 9 (82%) eventually became obese and suffered multiple endocrine deficits. The progression to morbid obesity and endocrine deficits can also occur after RT and during the natural course of tumor progression, but the manifestation is usually not acute.

When the tumor is infiltrative, extensive, and difficult to remove in bulk, hydrocephalus may be treated with a shunting procedure. Depending on the circumstances, one can consider either a ventriculoperitoneal or a ventriculocisternal (Torkildsen) type of shunt procedure.

In summary, we recommend a conservative surgical approach primarily for diagnosis. Once the diagnosis is made, children who exhibit favorable characteristics are followed up until signs of tumor progression occur. For those who show unfavorable characteristics (Table 5–2), either RT or chemotherapy is recommended for most, depending on the

age of the individual. For patients who have extensive tumors invading the hypothalamus, extending to the third ventricular region, with massive infiltration along the optic tracts, or with clear-cut evidence of rapidly progressive disease at the time of diagnosis, a delay in treatment is not recommended. However, in those few cases of tumors where surgical decompression and improvement of vision have occurred, especially in young children, very close follow up without intervention until objective signs of progression occur is also an acceptable alternative.

Radiation

Most modern reports utilizing megavoltage RT document an advantage for patients who have progressive chiasmal gliomas (Pierce et al., 1990; Horwich and Bloom, 1985; Wong et al., 1987; Tao et al., 1997). Radiation therapy is generally the treatment of choice for symptomatic chiasmatic/hypothalamic gliomas in older children. Many recent series report excellent survival after RT—generally 90% at 10 years (Pierce et al., 1990; Horwich and Bloom, 1985; Tao et al., 1997). However, deaths can occur from disease progression many years after treatment, and, thus, long-term follow up is critical in the management of this disease.

Outcome in terms of vision is an important measure of treatment success for chiasmal/hypothalamic gliomas. Following RT, vision is improved in approximately one-third of patients, with most patients experiencing visual stabilization (Pierce et al., 1990; Tao et al., 1997). This success in maintaining or improving vision is possible only if treatment is initiated before severe visual damage has occurred. Therefore, documented visual deterioration is a major indication for the prompt initiation of therapy.

The overall survival rate for patients with optic system gliomas is excellent. However, conventional RT has been associated with significant morbidity. Most radiation fields cover not only the tumor bed (tumor volume) but also tissues thought to be at risk for microscopic disease to allow for uncertainty in tumor definition and for inconsistencies in the daily treatment set-up (target volume). The tolerance of the normal brain parenchyma and its vascular and supporting structures becomes, therefore, the limiting parameter of external-beam therapy, and the risks of acute and long-term sequelae are major dose-limiting factors. Permanent radiation injury can include pituitary-hypothalamic dysfunction as well as memory and intellectual deficits. Young children are at greater risk than adults (Glauser and Packer, 1991; Ellenberg et al., 1987; Ater et al., 1999). After irradiation, 72% of children treated at the Joint Center for Radiation Therapy developed new onset of hypopituitarism, most commonly growth hormone deficiency in 59%, with panhypopituitarism in 21% (Tao et al., 1997).

With conventional fractionation schedules (1.8 Gy/day), total doses of 50 to 54 Gy are considered standard for the treatment of optic gliomas. Late effects appear in a predictable manner in terms of radiation dose, volume, and fractionation. Fractionation exploits the differences in response to irradiation between normal brain and tumor tissue; normal tissues tolerate multiple small doses of irradiation much better than they tolerate a single, large fraction.

Until recently, greater precision in the delivery of conventional RT was limited by an incomplete diagnostic definition of tumor volumes, unsophisticated treatment planning systems, and imprecise immobilization devices. Computed tomography and MRI now provide much improved delineation of CNS neoplasms, and three-dimensional treatment planning systems are currently available. These technological advances allow for accurate focal administration of a dose to the target area and have thus promoted the widespread use of radiosurgery techniques.

Stereotactic Radiosurgery

Stereotactic radiosurgery is a highly accurate and precise technique that utilizes stereotactically directed convergent beams of ionizing radiation to treat a small and distinct volume of tissue with a single radiation dose. The multiple-beam approach of radiosurgery results in sharp dose fall-off beyond the target, thus sparing adjacent normal tissue. The technique must, however, be reserved for select small lesions because it ablates both normal and abnormal tissue within the treatment volume. Some investigators have advocated using stereotactic radiosurgery to reduce the treatment volumes of discrete, well-circumscribed lesions, although certain parameters, including the size and location of the target volume, are associated with complications from radiosurgery (Marks and Spencer, 1991; Loeffler and Alexander, 1993; Tishler et al., 1993). Certain intracranial lesions cannot be treated safely or effectively with ra-

diosurgery once the target volume becomes relatively large or is located near brain stem, retina, and the optic pathways. For example, the maximum radiation tolerance of the optic nerve appears to be between 8 and 10 Gy; if more than 1 cm of the eighth nerve is treated with radiosurgery, hearing loss is predictable even with doses as low as 15 Gy (Tishler et al., 1993). Kjellberg and others have published isoeffect data predicting the incidence rates of brain necrosis using a proton facility (Kjellberg et al., 1983; Flickinger, 1989). These isoeffect curves demonstrate the relationship between tumor necrosis, radiation dose, and field size and demonstrate the limitations of using large single fractions for intracranial lesions that involve critical structures such as the optic system. Therefore, although stereotactic radiosurgery is precise in the administration of large single fractions, complications associated with larger volumes (greater than 3 cm) and with certain locations (brain stem, visual pathways) limit the use of this procedure in the primary management of pediatric tumors, particularly in the management of patients with optic pathway tumors.

Stereotactic Radiotherapy

Fractionation of the daily dose of radiation combined with the precision of radiosurgical techniques may be the optimal way to treat relatively small, symptomatic optic tumors that do not show extensive involvement along the optic tracts. Stereotactic RT is defined as the use of stereotactic radiosurgery hardware and software (stereotactic head frame and support system, small-field collimators, and three-dimensional planing) combined with radiation routine fractionation (1.8 Gy/day) or some form of altered fractionation such as hypofractionation (a few large fractions of 4.0 to 8.0 Gy). Basic requirements necessary to administer stereotactic RT include specially designed software and reproducible repeat head fixation and localization systems.

Dose-optimization treatment using stereotactic RT or other conformal techniques has now become routine for lesions that are well controlled by conventional RT. These RT techniques may become the treatment of choice for many diseases such as incompletely resected craniopharyngioma, pituitary adenoma, and small optic pathway tumors. The radiation dose to nearby nontarget volume structures vital for memory (mesial temporal lobe), for endocrine function (hypothalamic-pituitary axis), and for normal structural development (skull, mandible, and soft tissues of the scalp) is markedly reduced with these techniques. This technique of dose optimization is particularly important in the pediatric population. For many pediatric intracranial tumors, focal RT techniques will largely replace conventional RT in order to reduce the long-term side effects of therapy (Dunbar et al., 1994; Loeffler et al., 1999).

In general, the use of stereotactic techniques as definitive treatment should be restricted to lesions that *(1)* are distinct on imaging scans, *(2)* are of relatively small volume, and *(3)* are noninvasive or noninfiltrating. Although stereotactic techniques do not replace large-field RT in the treatment of widely infiltrating or seeding tumors, it is clear that conventional RT is no longer "acceptable" for a large subgroup of patients who have more focal intracranial tumors.

Chemotherapy for Optic Chiasmal Tumors

The use of chemotherapy for low-grade astrocytomas in children, especially optic chiasmal-hypothalamic tumors, has been investigated at several medical centers. In 1977, Packer and the group at Children's Hospital of Philadelphia started to treat patients younger than 6 years of age newly diagnosed with intracranial visual pathway gliomas with combination chemotherapy. Their justification for this approach was that the beneficial effects of radiation on vision could not be confirmed in their patient population as only 1 of 21 children demonstrated visual improvement after RT (Packer et al., 1983). In addition, these investigators found that progressive neurologic deterioration and visual loss did occur in patients who received radiation late in the course of their disease, usually 5 to 10 years after diagnosis.

Between 1977 and 1988, 32 children younger than 6 years of age were treated with vincristine and actinomycin D chemotherapy as initial therapy after diagnosis. At last report, 10 (31%) remained free of progressive disease and had not required additional therapy (Janss et al., 1995). For those whose disease progressed, the median time was 27 months after the initiation of treatment. Ten year overall survival for the entire group was 85% because of the success of salvage treatment.

Various chemotherapeutic agents, including lomustine; vincristine; a combination of procarbazine,

lomustine, and vincristine; and cisplatin-containing combinations, have been somewhat effective in patients with recurrent low-grade gliomas (Edwards et al., 1980) and have been utilized for optic chiasmal tumors. In an M. D. Anderson Cancer Center trial of nitrogen mustard, vincristine, procarbazine, and prednisone (MOPP) given to children younger than 3 years of age with low-grade astrocytomas; six children either had hypothalamic or brain stem lesions. With a median follow up of more than 7 years, all patients survived with stable disease. However, five of six eventually received RT for tumor progression at a median of 1 year after diagnosis (Ater et al., 1988).

Combination chemotherapy with 6-thioguanine, procarbazine, dibromodulcitol, lomustine, and vincristine has been substituted effectively for RT for children with chiasmal and hypothalamic astrocytomas. Investigators at the University of California at San Francisco (Petronio et al., 1991) initially reported results for 19 infants and children (median age, 3.2 years) with chiasmal and hypothalamic gliomas who received chemotherapy, 12 at diagnosis and 7 at the time of tumor progression. Most received 6-thioguanine, procarbazine, dibromodulcitol, lomustine, and vincristine chemotherapy, and two received other combinations. Of the 18 patients with evaluable disease initially managed with chemotherapy, tumors in 15 (83%) either responded to therapy or stabilized. With a median follow-up period of 18 months, all are surviving; disease progressed in only 4 of 15 and was successfully treated with radiation. Vision initially improved or stabilized in 16 (88%) patients. This series was updated in 1997 and now includes a group of 42 children with a mean age of 5 years. The median time to progression was 132 weeks, with a 5 year survival rate of 78% (95% CI, 60% to 87%) (Prados et al., 1997).

In low-grade hypothalamic and chiasmal gliomas, the criteria used to evaluate the usefulness of the chemotherapy are different from those in the usual phase II studies that assess tumor response. For low-grade astrocytomas, prolonged stable disease has been considered a "response" by some investigators. Friedman and the Pediatric Oncology Group (1992) studied the response of pediatric brain tumors to carboplatin. Based on results from 13 children with clearly progressive, low-grade astrocytomas of the optic pathway, third ventricle, thalamus and suprasellar region, and temporal region, in which 73% achieved stable disease and one had a partial response, Friedman's group determined that carboplatin is active against low-grade astrocytomas. The duration of stable disease in this subgroup of patients ranged from 3 months to greater than 68 months (median, >40 months).

A multi-institutional group studied the combination of weekly low-dose carboplatin plus vincristine given for low-grade gliomas (Packer et al., 1993, 1997). At the most recent report, 78 children with newly diagnosed progressive low-grade gliomas with a median age of 3.1 years were treated with this regimen. Fifty-eight were chiasmatic-hypothalamic in location, and the remainder occurred in other locations. Forty-five (56%) children had objective tumor response. Tumor response did not correlate with length of disease control. The only significant factor predictive of outcome was age, with a 2-year progression-free survival rate for children younger than 5 years at start of treatment of 81% compared with 58% in older children ($p < 0.01$) (Packer et al., 1997).

Partly because of variability in prognostic factors such as age, the most effective regimen cannot be gleaned from these single-arm studies. Therefore, a national randomized trial in the Children's Cancer Group (CCG) is currently underway testing the efficacy of chemotherapy for progressive low-grade gliomas in children younger than 10 years old, comparing the carboplatin-vincristine regimen to the CCNU-based regimen reported by Prados et al. (1997). Neuropsychological and endocrine outcome of children treated with chemotherapy will also be evaluated in this trial.

Long-term Follow-up and Complications of Therapy

The use of chemotherapy for hypothalamic-chiasmal gliomas is gaining support not only because of the previously mentioned risks of extensive surgery but also because of the consequences of conventional RT. For young patients, there is a risk of increased endocrine deficits and intellectual impairment following RT delivered to the hypothalamic region (Moore et al., 1992; Ater et al., 1997, 1999; Tao et al., 1997). Serial IQ scores before radiation showed no decline, but among those receiving radiation, IQ scores fell a median of 12 points from baseline (Janss et al., 1995). Also, several reports (Rajakulasingam et al., 1979; Mitchell et al., 1991) have recognized the risk

of radiation-induced moyamoya vascular change in the suprasellar region, which can result in vasospasm, transient ischemic-type episodes, seizures, and strokes. The actual incidence of moyamoya is not known, but it may be higher than suspected because the symptoms may also be attributed to progressive disease. The risk of moyamoya appears to be related to the patient's age at radiation, and the condition has been seen generally in children receiving radiation before 3 years of age or in association with neurofibromatosis type 1 (Poussaint et al., 1995).

When patients experience new symptoms that suggest progressive disease, especially many years after treatment, MRI or CT scans can provide essential information, but definitively distinguishing progressive disease from another cause can remain difficult. At times the MRI scan can be diagnostic, revealing hemorrhage, stroke, or tumor growth. However, in a report by Epstein et al. (1992), three children with chiasmatic-hypothalamic gliomas who had symptoms of tumor progression 9.5, 11.5, and 2 years after RT were found to have misleading radiographic findings. Neuroradiographic studies including angiography showed large mass lesions. These were presumed to be tumor recurrences and chemotherapy was initiated. However, on autopsy of two and biopsy of the third, the bulk of the mass was found to consist of numerous vessels of variable size. The authors proposed that these lesions probably represented "incorporation of the rich vasculature in the chiasmal region into the tumor, which underwent degeneration secondary to radiation therapy" (Epstein et al., 1992). Further prospective evaluation of the vascular phenomenon associated with these tumors and their treatment is needed.

MENINGIOMAS

Clinical Presentation

Meningiomas can occur anywhere within the cranium and are related to the arachnoid cap cells of the pacchionian granulations, where spinal fluid is absorbed into the venous sinuses. Meningiomas arise from these structures and are attached to the dura. They occur most commonly in females, and several different subtypes of meningioma can specifically affect the visual apparatus and the hypothalamus. Arising peripherally, meningiomas may grow out of the optic nerve sheath itself. These tumors tend to involve the dura of the optic nerve and ultimately strangulate the nerve; they may also occlude the blood supply to the ophthalmic artery. Direct surgery on these tumors usually results in devascularization of the optic nerve and blindness. The indications for surgery are progressive visual loss and proptosis, similar to the scenario with optic nerve gliomas but with a less favorable prognosis, as meningiomas can extend readily from the intraorbital segment of the optic nerve sheath through the optic canal to involve the intracranial dura.

Meningiomas may also arise from the dura around the optic foramen in which case these lesions may strangulate the optic nerve and affect the ophthalmic artery. Both optic nerve sheath meningiomas and meningiomas of the optic foramen can be bilateral. This is most commonly seen in optic foramen meningiomas where tumor cells may bridge from one optic foramen to the other or may arise as two separate, nearly symmetric, lesions around the optic foramen. More common are meningiomas that arise from the dura of the planum sphenoidale or the tuberculum sellae. The former cause optic nerve-type visual loss, compressing the optic nerves from above and pushing them inferiorly. The latter tend to be suprasellar tumors and may affect either the optic nerves or the optic chiasm or both. Some meningiomas arise from the dura of the diaphragma sellae and also act like suprasellar tumors, producing chiasmal-type visual loss and sometimes compressing the pituitary stalk, causing distortions of pituitary-hypothalamic function. Tumors arising from the dura of the inner third of the sphenoid wing commonly involve both the cavernous sinus (and the nerves within it) and the optic nerve on the same side. Patients afflicted with these tumors may present with double vision, ptosis, pupillary abnormalities, and optic nerve-type visual loss.

Management

Diagnosis

As with gliomas affecting the optic nerves and chiasm, patients with meningiomas in similar regions need careful documentation of their visual function and visual fields. Basic laboratory tests that include hormonal evaluations are important. The diagnostic imaging method of choice is an MRI scan with

gadolinium contrast, which clearly shows the meningioma and frequently its areas of origin from the dura. Such scans accurately reveal the effects of the tumor on the surrounding anatomy and help guide the surgeon in devising a safe and effective approach.

Surgery

Indications for surgery of meningiomas generally are those of progressive enlargement of the tumor along with the progressive visual and neurologic signs that may accompany such growth. A number of meningiomas reach a certain size and stop growing, so an argument can be made for careful follow up in some cases.

Basic surgical principles include the planning of a craniotomy that provides excellent exposure of the lesion with the ability to protect and preserve normal neurologic structures. Adjuncts such as intraoperative corticosteroids and mannitol to shrink the brain temporarily are most helpful, and the surgery is carried out with precise microsurgical techniques. Occasionally, a laser or ultrasonic surgical aspirator allows the surgeon to manage difficult tumors that may have a very firm consistency.

Because the vast majority of meningiomas are benign, surgery may not be indicated for patients whose vision is preserved without it when curative surgery could produce blindness or other forms of neurologic deficit. In such instances, RT has been beneficial in a reasonable number of patients.

Radiation Therapy

The largest use of radiation for menigiomas has been with conventional RT (Goldsmith et al., 1994). Postoperative RT is indicated for malignant menigiomas, subtotally resected tumors, tumors with atypical histologies, or multiply recurrent meningiomas. Focused radiosurgery also has its role in the management of small meningiomas, and many promising results have been reported (Hakim et al., 1998).

CRANIOPHARYNGIOMA

Clinical Presentation

Craniopharyngiomas are developmental lesions thought to arise from squamous remnants of Rathke's pouch. Although these tumors tend to appear as tumors of childhood, they can actually occur at any age; there are three basic types of clinical presentation that are age related. In childhood, craniopharyngiomas tend to be large, cystic suprasellar lesions that present as failure of growth and development, which are related to the tumor's effects on the hypothalamus. Craniopharyngiomas may also present with progressive visual loss of the chiasmal type along with obstructive hydrocephalus in large lesions that affect the third ventricle. In young adulthood, craniopharyngiomas tend to present in a fashion similar to pituitary adenomas. In women, the amenorrhea-galactorrhea syndrome is a common presentation and may or may not be associated with progressive chiasmal-type visual loss. Men may develop hypopituitarism and impotence along with visual symptoms. In the elderly, these tumors usually present with mental function changes, but may also produce increased intracranial pressure and visual loss.

Management

Diagnosis

Medical evaluation for craniopharyngiomas should include a careful history and physical examination, paying particular attention in children to their growth and development, including secondary sexual characteristics, and to sexual function in older patients. Careful evaluation of the visual system, including visual acuity and visual field determinations, should be carried out. Laboratory evaluation should include a careful review of pituitary hormone status. Because craniopharyngiomas frequently arise from the pituitary stalk, some patients, particularly children, present with diabetes insipidus; appropriate laboratory tests should be ordered if this is one of the features of clinical presentation.

Patients with increased intracranial pressure usually have headaches and may have papilledema. The imaging procedure used for diagnosis is an MRI scan with gadolinium contrast. This modality usually is fairly diagnostic for craniopharyngioma. Because many of these lesions are calcified, a CT scan or even a plain skull X-ray may show the presence and position of calcified portions of the tumor. For the evaluation of postoperative residual disease, CT and MRI scans are often complementary, with CT demonstrating residual calcification (not easily seen on MRI) and MRI most often demonstrating possible residual cystic or solid craniopharnygioma.

Surgery

The surgical principles utilized in the management of craniopharyngioma are a subject of some controversy. It is clear that a proportion of these lesions, particularly cystic lesions in children, can be totally excised. Ordinarily this is accomplished using a craniotomy for those lesions that are suprasellar. The craniotomy procedure utilized to attack a craniopharyngioma can be tailored to the position and extent of the lesion. Subfrontal, frontotemporal (pterional), and a variety of skull base approaches can be utilized to approach and effectively remove these lesions. A scrupulous microsurgical technique is essential and can provide good results in both extent of tumor removal and preservation or restoration of vision. If a craniopharyngioma is associated with significant enlargement of the sella, then the tumor may have had its origin below the diaphragma sella and may be amenable to total removal using the transsphenoidal approach. For these lesions, the size of the sella, whether the tumor is primarily cystic or primarily solid, and whether calcifications are present can be important factors in determining the extent of debulking. Many suprasellar craniopharyngiomas, particularly in older patients, are intimately associated with the floor of the third ventricle, the hypothalamus, and the optic chiasm. In such cases, attempts at total removal can produce significant neurologic damage; thus the surgeon must use good judgment in attempting complete tumor removal. Often, it is better to remove the bulk of the tumor and to treat the small remnants adherent to vital structures with postoperative irradiation.

Radiotherapy

Conventional RT has been effective for craniopharyngiomas (Hetelekidis et al., 1993). For the reasons stated previously, however, conventional RT is not recommended for the immature brain (generally, children 3 years of age or younger). Stereotactic techniques include radiosurgery, stereotactic RT, and direct colloid instillation into cystic craniopharyngiomas. Radiosurgery has been utilized for adjunctive management of craniopharyngiomas. However, because the chiasm is often in close proximity, the same constraints as discussed earlier apply for craniopharyngiomas (Tarbell et al., 1994).

Radiosurgery should only be considered when there is a very small area (less than 2 cm) of residual/recurrent tumor that is away from the optic chiasm. Direct instillation of colloidal radioisotopes into the cysts of primarily cystic tumors appears effective when appropriately applied. This technique has been widely used in Europe with limited experience in the United States. Stereotactic radiation or conformal radiation treatments using conventional fractionation may be the safest mode of treatment for patients with a solid component of residual disease.

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