

Advances Toward an Understanding of Brainstem Gliomas

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A B S T R A C T

The diagnosis of brainstem glioma was long considered a single entity. However, since the advent of magnetic resonance imaging in the late 1980s, neoplasms within this anatomic region are now recognized to include several tumors of varying behavior and natural history. More recent reports of brainstem tumors include diverse sites such as the cervicomedullary junction, pons, midbrain, or the tectum. Today, these tumors are broadly categorized as either diffuse intrinsic gliomas, most often in the pons, or the nondiffuse brainstem tumors originating at the tectum, focally in the midbrain, dorsal and exophytic to the brainstem, or within the cervicomedullary junction. Although we briefly discuss the nondiffuse tumors, we focus specifically on those diffuse brainstem tumors that regrettably still carry a bleak prognosis.

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EPIDEMIOLOGY

Brainstem gliomas account for approximately 20% of all CNS tumors among children younger than age 15.¹ This increase from 10% in the late 1970s reflects an increase in detection of the nondiffuse brainstem tumors by magnetic resonance imaging (MRI) rather than a true increase in incidence. The median age at presentation for all brainstem gliomas in children is 6 to 7 years, with males and females equally affected.² Among adults, brainstem gliomas are considerably less common, but reported up to age 70 years, sometimes with a less aggressive course. There is an increased frequency of brainstem tumors among patients with neurofibromatosis type 1, and these tumors have a more indolent behavior.^{3,4}

ANATOMY AND FUNCTION

The human brainstem comprises three connected parts: the midbrain, pons, and medulla, each composed of numerous axonal tracts (white matter), cranial nerve nuclei, and noncranial nerve brainstem nuclei (gray matter). Thus, the brainstem serves as the conduit through which axonal tracts pass to the spinal cord, cerebrum, or exit as cranial nerves. Within the brainstem, axonal tracts course in longitudinal, oblique, and transverse directions and may synapse within the brainstem nuclei. Newer imaging techniques such as diffusion tensor imaging allow these white matter tracts to be visualized. Neurologic deficits resulting from brainstem tumors result from mass effect or invasion of white matter tracts or nuclei.

Midbrain gray matter includes the periaqueductal gray circumferential around the aqueduct of

Sylvius and reticular formation in the tegmentum. Tumors arising in this area tend to be lower grade and focal, and may cause aqueductal obstruction and subsequent hydrocephalus. The reticular formation extends the length of the dorsal brainstem, controlling vital functions such as blood pressure and respiration, while also regulating general level of alertness. Oculomotor (III) and trochlear nuclei (IV) reside in the midbrain. The third nerve exits ventrally from the medial aspects of the crus cerebri in the interpeduncular fossa. Lesions of the oculomotor nerve result in external strabismus, ptosis, and dilation of the pupil from loss of parasympathetic innervation of the radial muscles of the iris. The fourth cranial nerve exits the posterior brainstem near the lower margin of the inferior colliculus. An isolated lesion of the trochlear nerve results in failure of downward gaze when the eye is turned to the nose and a patient may complain of vertical or skew (diagonal) diplopia. The tectum of the midbrain is dorsal to the aqueduct of Sylvius and contains nuclei within the superior and inferior colliculi, which participate in visual and auditory processing, respectively. Tectal tumors are typically low-grade lesions, often affecting the cerebral aqueduct.

In addition to the reticular formation, gray matter structures in the pontine tegmentum include the trigeminal (V), abducens (VI), facial (VII), and vestibulocochlear (VIII) cranial nerve nuclei. Numerous unnamed pontine nuclei reside in the basilar pons. The nuclei of the trigeminal nerve are large, with a motor nucleus in the pons and sensory nuclei extending from the midbrain to the upper cervical spinal cord. The three divisions of the trigeminal nerve exit the lateral pons superior to the middle cerebellar peduncle. The motor nucleus controls muscles of mastication while larger sensory

components distribute to the face, mouth, nasal cavity, orbit, anterior half of the scalp, and dura matter.

Cranial nerves VI, VII, and VIII exit the brainstem anteriorly near the pontomedullary junction. The abducens nerve is susceptible to injury because it has the longest intracranial course passing between two layers of dura on the floor of the posterior fossa, to the cavernous sinus, and innervates the lateral rectus muscle after passing through the superior orbital fissure. Injury to the abducens nerve results in horizontal diplopia. Injury to the facial nerve results in ipsilateral facial weakness and loss of corneal reflex when the lesion is peripheral. In addition, when seventh nerve injury is proximal or in the cerebellopontine angle, ipsilateral hyperacusis, absent taste sensation in the anterior tongue, and disturbed secretion of tears and saliva are present. Tumors within the pons are often diffuse, infiltrative of white matter, and effect adjacent cranial nerves and white matter tracts passing through the brainstem.

Gray matter structures in the medulla include the dorsal sensory nuclei and the nucleus ambiguus, in the anterolateral part of the reticular formation. Motor fibers from this nucleus leave the medulla as fibers of the glossopharyngeal nerve (IX), vagus (X), and bulbar accessory (XI) nerves. Lesions of these nuclei or nerves affect swallowing and vocalization and exit the medulla in the dorsolateral medullary groove. The hypoglossal nucleus (XII) is located medially in the inferior medulla and innervates ipsilateral striated muscle of the tongue after exiting from the ventrolateral medullary groove. The dorsal motor nucleus of the vagus nerve (X) is located lateral to the hypoglossal nucleus and is an important part of the parasympathetic nervous system. Inferior vestibular nuclei (VIII) are positioned dorsolateral in the medulla near the anterior fourth ventricle.

PATHOLOGY

Diffuse intrinsic tumors account for approximately 80% of all brainstem gliomas.⁵ These tumors are generally high-grade anaplastic astrocytoma (WHO grade 3), glioblastoma multiforme (WHO grade 4), or occasionally, well-differentiated diffuse astrocytoma (WHO grade 2).² At autopsy, most pontine tumors are high-grade gliomas and may disseminate within the neuraxis.^{6,7} In contrast, the focal, the dorsal exophytic, and the cervicomedullary tumors are pilocytic astrocytomas (WHO grade 1) or, less often, ganglioglioma (WHO grade 1) or diffuse astrocytoma (WHO grade 2).^{2,8} Because of their anatomic location, it is often difficult to obtain tissue for histopathologic confirmation of tumor type and grade.

The differential diagnosis for a brainstem tumor at an atypical age, or with an unusual presentation or neuroimaging also includes the atypical teratoid-rhabdoid tumor as well as the embryonal tumors, (ie, primitive neuro-ectodermal tumor).^{9,10} Hemangioblastoma is less common, and occurs in adolescents or adults, particularly in association with von Hippel-Lindau disease. Vascular malformation, demyelinating disease, and focal brainstem encephalitis seldom masquerade as a brainstem tumor.

CLINICAL PRESENTATION

The most common presentation of a brainstem glioma is that of the diffuse brainstem glioma, rising in the pons and causing diffuse en-

largement. Patients typically report a short duration of symptoms, median one month, and have a triad of signs including cranial neuropathy, long tract signs (hyperreflexia, a Babinski sign, and weakness), and cerebellar signs (ataxia, dysmetria, or dysarthria). The cranial nerve impairment is often with multiple, unilateral or bilateral, cranial nerve deficits, particularly cranial nerve VI and VII paresis. The tumor commonly engulfs the basilar artery, and many have axial or exophytic extension to the midbrain, cerebral peduncles, cerebellum, or medulla. Hydrocephalus and metastatic disease from diffuse tumors of the pons are rare.

In contrast, patients with a focal brainstem tumor have a more insidious presentation, with a long history of localizing signs, such as isolated cranial nerve deficit and contralateral hemiparesis. Elevated intracranial pressure is uncommon. These tumors are usually discrete, well circumscribed, and often times dorsal and exophytic, adjacent to or arising from the floor of the fourth ventricle. They may also involve the medulla or the midbrain, and may present with emesis and failure to thrive. Tumors arising in the tectal region obstruct the aqueduct of Sylvius, causing increased intracranial pressure and hydrocephalus.

NEUROIMAGING

High-quality MRI of brainstem tumors is essential in clinical management to localize the lesion and to differentiate focal from diffuse tumor involvement. A focal tumor is typically well marginated, enhances with contrast, and occupies less than 50% of the axial diameter of the midbrain or medulla (Fig 1). A diffuse tumor is poorly marginated, rarely enhances, occupies more than 50% of the axial diameter of the pons and commonly engulfs the basilar artery (Fig 2). The diffuse



Fig 1. Sagittal T2 weighted magnetic resonance image demonstrating a well circumscribed, low-grade, dorsally-exophytic brainstem tumor. (*) Indicates the solid portion of the tumor enhanced homogeneously on T1 weighted images, while the cystic portions of the tumor above and below enhanced less.

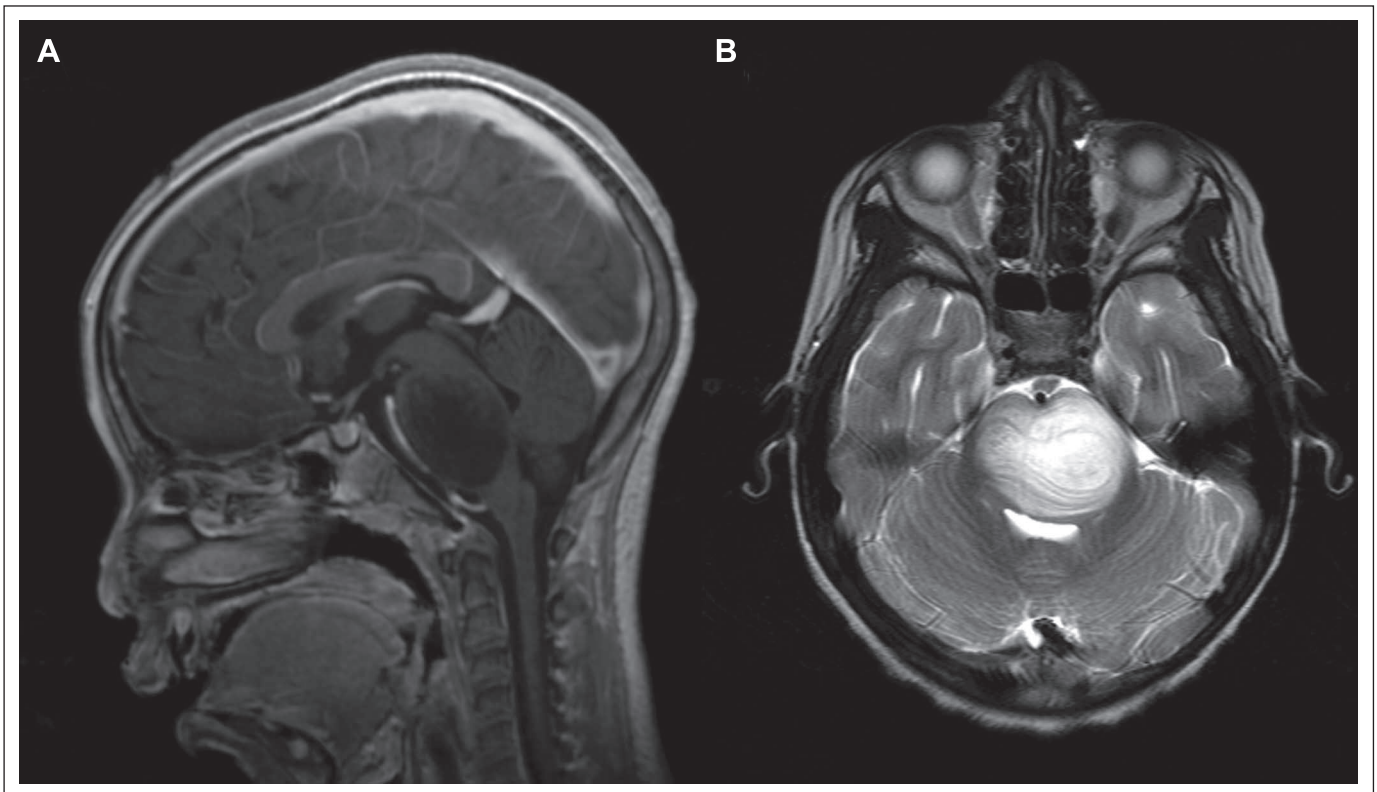


Fig 2. Sagittal T1 magnetization prepared rapid gradient echo (A) and axial T2 weighted; and (B) magnetic resonance images showing the infiltrative nature of a diffuse brainstem glioma as it involves the entire pons. The left pons is more expanded as the tumor infiltrates between transverse bands of darker, myelinated white matter tracts.

tumor, which infiltrates and expands the brainstem, is shown as increased signal on T2-weighted MRI sequences.

Treatment-related changes may be difficult to differentiate from progressive disease. Early cystic or necrotic changes within 3 to 4 months of radiation therapy often represent treatment effects. As intralesional hemorrhage may occur spontaneously or following irradiation, imaging studies should include pulse sequences sensitive to detecting intratumoral bleeding (eg, gradient echo sequences). Computed tomography brain scans can also be useful in detecting and characterizing intralesional bleeding.

Prospective studies testing new imaging technology such as perfusion and diffusion MR sequences, MR spectroscopy (MRS), and positron emission tomography (PET) are accumulating data helpful to differentiate treatment change from disease progression.¹¹ These imaging methods provide quantitative physiologic and functional information to complement the anatomic visualization provided by conventional imaging. Imaging protocols addressing perfusion and metabolic characteristics of diffuse brainstem tumors are under study by the Pediatric Brain Tumor Consortium.

MR perfusion measures regional blood volume and flow reflecting the vascular nature of neoplasms.¹² Serial changes in tumor vascularity may be a valuable method to monitor effectiveness of therapy, especially as new biologic agents with antiangiogenic properties are introduced. Diffusion tensor imaging provides visualization and quantitative characterization of the major white matter pathways in the brain (Fig 3). It has been used to study supratentorial tumors,¹³⁻¹⁹ and recent studies demonstrate its value in brainstem lesions to guide operative intervention in focal low-grade gliomas, and to characterize

white matter tracts in the diffuse gliomas.^{20,21} Figure 3 shows diffusion tensor imaging with color hue demonstrating the principal direction of anisotropic water diffusion in white matter tracts: normal axonal tract orientation in the pons; corticospinal tracts, transverse pontine (TP) tracts, middle cerebellar peduncles, and tracts of the central tegmentum; tumor within the fourth ventricle changing tract orientation in the tracts of the central tegmentum and middle cerebellar peduncles; tumor expanding the TP tracts, but not affecting direction; and tumor expanding the pons with loss of direction in the TP tracts suggesting invasion and destruction of axon fibers.

Proton MRS may provide insight into the biology of brainstem tumors based on the small set of metabolites detected in the human brain.²² The most prominent peaks in the brain spectrum are *N*-acetyl aspartate, creatine, and choline. NAA is a neuronal marker and is generally decreased in tumors. The creatine peak includes creatine and phosphocreatine and is often equal to, normal or diminished in neoplastic tissue. Choline reflects the metabolism of membrane turnover, and often is increased in tumors. In addition, peaks from lactate and mobile lipids are often elevated in malignant tumors, especially with necrosis. MRS is being used to differentiate brainstem glioma from brainstem enlargement associated with neurofibromatosis type 1.²³

[¹⁸F]fluorodeoxyglucose (FDG)-PET scanning has not been widely applied to the study of brainstem tumors. The principle indications for FDG-PET are to distinguish viable tumor from post-therapeutic changes and to detect tumor transformation to a higher grade. High FDG accumulation compared with adjacent brain indicates residual or recurrent tumor, whereas low or absent FDG uptake is observed in areas of necrosis. However, FDG-PET findings are not

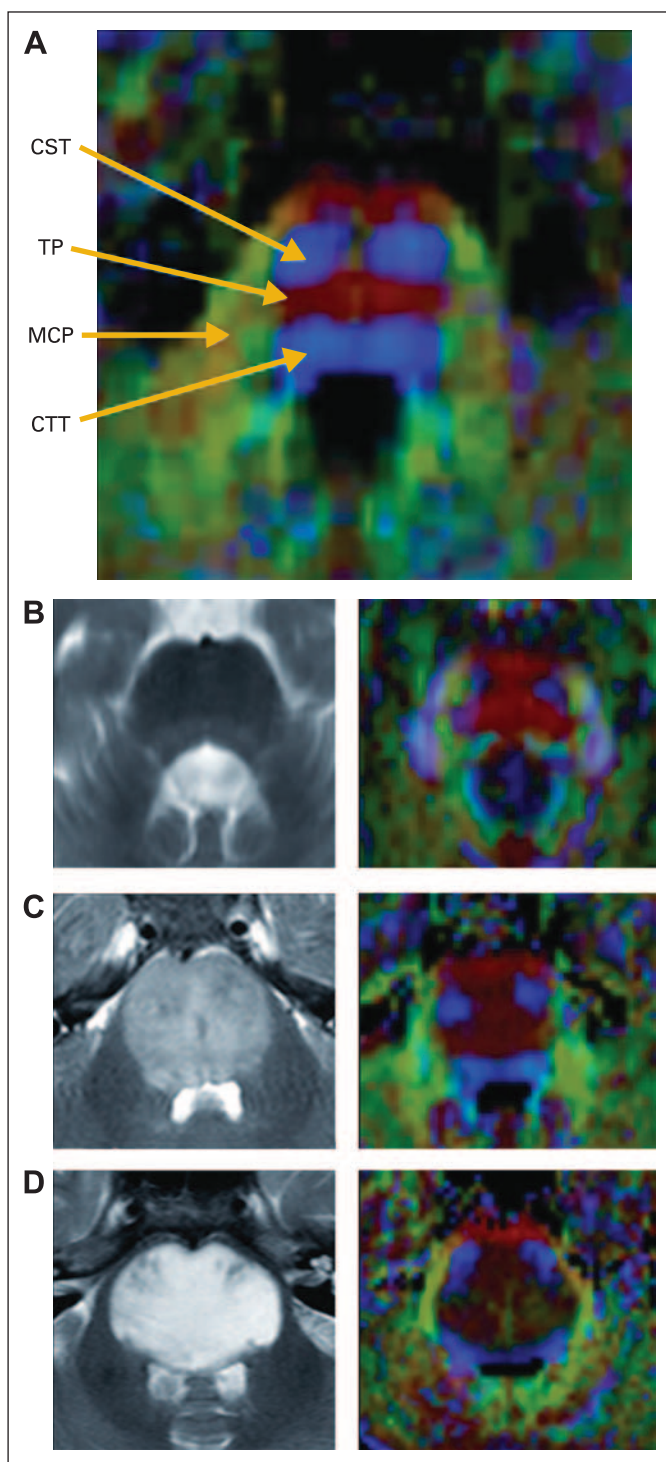


Fig 3. Diffusion tensor imaging (DTI) color-mapped images compared with corresponding T2-weighted axial images. (A) DTI from a normal adult volunteer; normal axonal tract orientation in the pons; corticospinal tracts (CST), transverse pontine (TP) tracts, middle cerebellar peduncles (MCP), and tracts of the central tegmentum (CTT); (B) DTI from a patient with cervicomedullary juvenile pilocytic astrocytoma; (C) DTI from a patient with a diffuse pontine glioma; and (D) DTI in a patient with a diffuse pontine glioma with pontine expansion. Blue depicts tracts oriented in craniocaudal direction, red shows right to left, and green shows anterior to posterior. Color intensity indicates the degree of diffusion anisotropy.

consistent in differentiating tumor from treatment effects. Other tracers may prove more useful in the study of brainstem gliomas. Carbon-11 methionine PET images show higher tumor to nontumor ratios in CNS tumors than FDG images do. Other tracers for future study include ^{18}F -fluoro thymidine, a marker of DNA synthesis and cellular replication (B.L. Shulkin, personal communication, September 2005).

TREATMENT

The choice of therapy for a brainstem glioma rests largely on whether the tumor is diffuse or nondiffuse. Prognosis for a patient with a diffuse brainstem tumor is poor, with median survival less than 1 year and less than 20% of children alive by 2 years.⁵ Conventional radiotherapy is standard treatment; the role of chemotherapy, radiosensitizing, and other biologic agents remain unclear. Among the nondiffuse tumors, there is a relatively good outcome with more than half of the patients surviving beyond 5 years. This finding and the site of the tumor affect selection of therapy.¹

Surgery

At present, surgery no longer has a role in the diagnosis or treatment of diffuse pontine glioma. The MRI findings at presentation are highly specific, and histologic findings do not influence treatment.²⁴ Meaningful resection is not possible, as the diffuse tumor is interwoven within white matter tracts traversing the brainstem and resection does not confer a survival advantage.^{25,26}

In contrast, some nondiffuse tumors, especially those that are focal or cystic, are surgically accessible with modern neurosurgical techniques.²⁷ Many patients may require no additional postoperative treatment, even after subtotal resection.²⁵ Extensive resection of a dorsal exophytic tumor, which leaves a layer of tumor on the surface of the brainstem, may prolong progression-free survival without additional treatment.^{8,25,28} Whether these surgical results are an improvement over those achieved with conventional local-field irradiation is unclear. A lesion confined to the tectum does not require resection or biopsy, simply shunt placement or third ventriculostomy on development of obstructive hydrocephalus, followed by close observation.²⁹ Such a patient may remain stable for years or decades, and seldom requires radiotherapy.

Radiotherapy

Radiotherapy had been the recommended treatment for all brainstem gliomas, but now is used more selectively. For a patient with a diffusely infiltrative brainstem glioma, standard treatment remains conventional external beam, local field radiotherapy to a dose of 54 to 60 Gy in 6 weeks. Without radiation, median survival is approximately 20 weeks.³⁰ Radiotherapy results in a worthwhile, albeit temporary, improvement in neurologic function, though the overall prognosis for such a patient remains dismal. Increasing the radiation dosage beyond 60 Gy has not proved effective. With hyperfractionation, using total doses of 64 Gy or higher, delivered in twice daily, smaller dose fractions over 6 weeks, failed to yield additional survival benefit.

For a patient whose focal brainstem glioma is of favorable low-grade pathology, radiotherapy may be delivered postoperatively to residual disease or deferred until there is disease progression.^{8,25} No controlled or prospective trials have been performed in these patients. For a patient whose tumor recurs after surgical resection, or for a

patient with a WHO grade 3 or 4 astrocytoma, radiotherapy should be considered. Radiotherapy should also be considered for a patient with a symptomatic or inoperable tumor.

Chemotherapy

Currently, there is little, if any, evidence to suggest that chemotherapy has affected the outcome of children with diffuse brainstem gliomas. Response rates to various single-agent and multiple-agent regimens have been disappointingly low, even when chemotherapy was given as initial treatment. Cytotoxic, biologic, or radiosensitizing agents have yet to improve outcome. For a focal brainstem glioma, weekly carboplatin with vincristine has shown activity in a limited number of young patients.³¹

CLINICAL TRIALS IN DIFFUSE BRAINSTEM GLIOMAS

For many years clinicians believed that brainstem tumors in children were so rare, and had such a poor prognosis, that it would be impossible to perform a national clinical trial. However in 1983, radiation oncologists from 13 institutions within the Pediatric Oncology Group (POG) participated in a questionnaire survey examining the results of radiation treatment over the 10-year pe-

riod January 1972 through December 1981. While the outcome of these 62 patients was disappointingly low, with 3-year survival of only 23%, several conclusions were apparent.³² The role of surgery was limited to confirmation of diagnosis, or volume reduction in selected patients, while radiotherapy was the mainstay of treatment. Failure of local control was the major obstacle to cure, with no evidence to support whole-brain or whole-craniospinal axis irradiation. Investigators soon realized that a cooperative group effort was needed to address serial questions regarding biology and treatment for children afflicted with these kinds of tumors.³² Thereafter a series of phase I/II trials were conducted in search for ways to improve results of treatment, including altered radiotherapy fractionation schedules, and other approaches such as the use of systemic chemotherapy in combination with radiotherapy and radiation sensitizers. Table 1 summarizes some of these trials. A series of radiation dose escalation studies used hyperfractionated radiotherapy (HRT) with doses from 64.8 Gy to 78 Gy, in a twice daily schedule with an interfractional interval of no less than 6 hours.³³⁻⁴⁵ At the highest radiation dose levels, corticosteroid dependency, vascular events, white matter changes, hearing loss, hormone deficiencies, and seizures were observed. These important studies demonstrated that lower-radiation doses would need to be used for future studies.

Table 1. Clinical Trials in Brainstem Glioma

| Trial Treatment | No. of Patients | Median Survival Time (months) | % Survival | | |
|---|-----------------|-------------------------------|------------|---------|---------|
| | | | 1 year | 2 years | 3 years |
| Conventional RT | | | | | |
| 36-60 Gy RT ^{32*} | 62 | | 50 | 29 | 23 |
| 20-55 Gy ^{33†} | 32‡ | 34 | | | 49 |
| 1.67-2.25 Gy fx | 21 adults | | | | |
| POG 8495 HRT | | | | | |
| 66 Gy in 1.1 Gy fx ^{5,34,35,36§} | 38 | 11 | 48 | 6 | 3 |
| 70.2 Gy in 1.17 Gy fx | 57 | 10 | 40 | 23 | 21 |
| 75.6 Gy in 1.26 Gy fx | 39 | 10 | 39 | 6 | 6 |
| SJCRH | | | | | |
| 70.2 Gy in 1.17 Gy fx + carboplatin + etoposide ³⁷ | 9 | 11 | 44 | 11 | |
| POG 9239 | | | | | |
| 54 Gy in 1.8 Gy fx + cisplatin ^{38¶} | 130 | 8 | 31 | 7 | 4 |
| 70.2 Gy in 1.17 Gy fx HRT + cisplatin | | | 17 | 7 | 5 |
| POG 8495 | | | | | |
| 70.2 Gy in 1.17 Gy fx HRT ³⁹ | 131 | 10 | 40 | | |
| POG 9239 | | | | | |
| 70.2 Gy in 1.17 Gy fx HRT + cisplatin | 130 | 8 | 27 | | |
| CHOP/NYU | | | | | |
| 64.8 Gy in 1.2 Gy fx HRT ⁴⁰ | 16 | 11 | 48 | | |
| 72 Gy in 1.0 Gy fx HRT ⁴¹ | 35 | | | 28 | |
| CCG 9882 | | | | | |
| 72 Gy in 1 Gy fx HRT ^{41,42,43} | 53 | 9 | 38 | 14 | 8 |
| 78 Gy in 1 Gy fx HRT | 66 | 9.5 | 35 | 22 | 11 |
| UCSF | | | | | |
| 72 Gy in 1 Gy fx HRT ⁴⁴ | 20 | 13 | | | |
| 78 Gy in 1Gy fx HRT ⁴⁵ | 39 | 10.8 | | | |

Abbreviations: RT, radiation therapy; Gy, gray; fx, fraction; POG, Pediatric Oncology Group; HRT, hyperfractionated radiation therapy; SJCRH, St Jude Children's Research Hospital (Memphis, TN); CHOP/NYU, Children's Hospital of Philadelphia (Philadelphia, PA)/New York University (New York, NY); CCG, Children's Cancer Group; UCSF, University of California, San Francisco (San Francisco, CA).

*Retrospective survey.

†Retrospective review including mid-brain, medulla, and cervical cord.

‡Patients were children.

§Phase I-II dose escalation study.

¶Phase III study infusional cisplatin as radiosensitizer.

||Patients receiving HRT + cisplatin fared worse than HRT alone.

A trial of concurrent carboplatin and etoposide with 70.2 Gy HRT did not improve outcome over radiation alone, with only 11% of patients with 2-year survival.³⁷ This experience plus an earlier study of adjuvant chemotherapy of lomustine, vincristine, and prednisone compared with conventional radiotherapy alone showed no improvement in survival with the addition of chemotherapy.⁴⁶ An important phase III randomized trial, POG 9239, tested radiation at the standard dose of 54 Gy in 1.8 Gy daily fractions versus 70.2 Gy in 1.17 Gy twice daily fractions, with all children receiving infusional cisplatin as a radiation sensitizer. There was no improvement in event-free survival or survival using HRT, thus leaving conventional radiotherapy as the radiotherapeutic regimen of choice for children with newly-diagnosed brainstem glioma.^{38,47} A comparison of children treated with 70.2 Gy HRT with or without cisplatin, demonstrated that patients receiving cisplatin plus HRT actually fared worse than those receiving HRT alone.³⁹ The addition of escalating doses of β interferon following HRT produced dose-limiting toxicity, but survival of less than 10%.⁴⁸ Groups have also tried approaches such as blood-brain barrier disruption (eg, the bradykinin RMP-7) and inhibition of drug resistance with cyclosporine to overwhelm P-glycoprotein mediated xenotoxin efflux.^{49,50} Novel approaches are worthy of continual clinical trials in children with diffusely infiltrative pontine tumors.

FUTURE INVESTIGATIONS

Effective experimental models and strategies that will improve survival for patients with diffuse brainstem gliomas are needed. At least three reasons account for our present lack of success. First, diffuse brainstem gliomas share some similarities in biology and behavior as the adult high-grade gliomas, where therapeutic advances have likewise been minimal.⁵¹ The median survival for an adult with cerebral glioblastoma is approximately 41 weeks. Secondly, the generation of biologic studies of these tumors is now hampered by the current practice of not

obtaining tissue for diagnosis. We cannot assume that biologic properties of brainstem tumors in children are completely identical to cerebral high-grade gliomas of adults. Limited prior studies using archival tissue from diffuse brainstem gliomas have demonstrated overexpression of the *erbB1* receptor and presence of *P53* mutations.^{52,53} However, our future potential to more fully characterize the genetic or molecular nature of diffuse brainstem gliomas via conventional molecular or genetic methods is now thwarted by a lack of specimens. Finally, the location of these tumors, where the vital architecture of white matter tracts and gray matter nuclei are compactly juxtaposed with brain matter, has made resection or the placement of therapy directly into the tumor essentially impossible.

Currently clinical trials employ chemotherapeutic and other biologic agents investigated in trials in adult gliomas, which unfortunately, are not sufficiently similar to the diffuse brainstem glioma of children. Nevertheless, immediate and future attention has turned to epidermal growth factor receptor signal inhibitors, antiangiogenesis agents (thalidomide), farnesyl transferase inhibitors, radiation sensitizers (gadolinium texaphyrin, arsenic trioxide), inhibitors of chaperone proteins (eg, 17-AAG), and histone deacetylase inhibitors (valproic acid). The Children's Oncology Group is studying the oral alkylating agent temozolomide concurrent with and following conventional radiotherapy, in an attempt to build on the small success demonstrated in adults with glioblastoma.⁵⁴ Phase I/II studies are being conducted in the Pediatric Brain Tumor Consortium with the EGFR inhibitor erlotinib and the farnesyl transferase inhibitor R115777.

Future advances in diffuse brainstem gliomas will likely require entirely new technological approaches. Advanced MRI techniques may begin to elucidate the biology of these tumors, especially over their clinical course. Local delivery of drugs by an osmotic pump is one example of an early effort to invoke novel engineering and an entirely different paradigm.⁵⁵ Whether bioengineering or nanotechnology can provide therapeutic success in this tumor remains to be determined.

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