Brainstem tumors: Current management and future directions

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ABSTRACT

Tumors arising in the brainstem comprise 10–20% of all pediatric central nervous system (CNS) tumors and account for a small percentage in adults. The prognosis for these tumors was considered uniformly poor prior to the era of modern neuroimaging and the location was fraught with disaster being considered a 'no man's land' for neurosurgeons. Following the introduction of advanced imaging modalities and neurophysiological monitoring, striking progress has occurred in the management of these lesions. Brainstem tumors are presently classified based on their anatomic location, focality, and histopathology. This article reviews the current classification of brainstem tumors, current management options, and future directions in the treatment for these rare tumors.

Key words: Brainstem glioma, brainstem tumors, cervicomedullary, dorsal exophytic tumors, management, medulla, midbrain tumors, pontine glioma, tectal tumors

INTRODUCTION

Brainstem tumors comprise 10–20% of all central nervous system (CNS) tumors in the pediatric population and account for less than 2% of intrinsic tumors.[1,2] There are approximately 150–300 cases diagnosed annually in the United States.[3,4] The typical age at diagnosis is between 7 and 9 years, although they can occur at any age without any gender predilection.[5,6] About 75% of brainstem neoplasms are diffuse gliomas, with focal lesions representing a minority. The outcomes for these tumors lie at two ends of a spectrum; diffuse gliomas have a poor prognosis, with median survivals ranging from 4 to 15 months[7] whereas focal tumors have a good prognosis,[8,9] with five-year, progression-free survival rates of 60% and overall five-year-survival of 89%.[10]

Historically, brainstem tumors were grouped together as a single entity with uniformly fatal outcomes, but it is now understood that their behavior depends on their anatomic location, focality, and histopathology. The early 1980s saw several neurosurgeons reporting favorable surgical outcomes for certain types of brainstem gliomas[11-15] and the introduction of various classification systems in an attempt to identify tumors that could be successfully treated with surgery. The introduction of magnetic resonance imaging (MRI) helped delineate tumor location and predict tumor behavior. A thorough understanding of brainstem tumor behavior based on location and imaging characteristics is essential in determining the appropriate management options.

Access this article online	
Quick Response Code:	Website: www.ijns.in
	DOI: 10.4103/2277-9167.94371

Imaging and Classification Schemes

Although previous classifications were created based on surgical observation and the use of computed tomography (CT),[13,15,16] the primary diagnostic modality for brainstem tumors is MRI.[17-19] The multi-planar MR images provide the most precise information regarding tumor epicenter, tumor diagnosis, and prediction of its biological behavior. Angiography, MRI spectroscopy or diffusion-weighted MRI sequences may be utilized[20,21] to improve the diagnostic accuracy in uncertain cases and have largely replaced the need for stereotactic biopsy.[22,23]

Early classifications categorized brainstem tumors into focal or diffuse. In general, focal tumors tend to be amenable to surgical resection while surgery is rarely indicated for diffuse tumors[24] [Table 1]. More composite schemes subdivide these tumors by location within the brainstem (midbrain, pons, and medulla), contrast enhancement pattern, presence or absence of exophytic growth in relation to brainstem, and presence

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Table 1: Classification systems for brainstem tumors

Author	Classification system	Imaging modality
Epstein F *et al.*, 1985[5]	Intrinsic Diffuse Focal Cervicomedullary Exophytic Anterolateral into cerebellopontine angle Posterolateral and into brachium pontine Disseminated Positive cytology Positive myelography	CT
Epstein F *et al.*, 1986[6]	Diffuse Focal Cervicomedullary	CT, MRI and surgical observation
Stroink AR *et al.*, 1987[7]	Group I – Dorsal exophytic glioma Group IIa – Intrinsic brainstem tumors Hypodense, no enhancement Group IIb – Intrinsic brainstem tumors Hyperdense, contrast enhancing, exophytic Group III – Focal cystic tumor with contrast enhancement Group IV – Focal intrinsic isodense, contrast enhancing	CT
Barkovich AJ *et al.*, 1990[9]	Location (midbrain, pons, medulla) Focality (diffuse of focal) Direction and extent of tumor growth Degree of brainstem enlargement Exophytic growth Hemorrhage or necrosis Evidence of hydrocephalus	MRI
Albright AL., 1996[8]	Diffuse Focal (midbrain, pons-intrinsic, dorsally exophtytic, medulla)	MRI
Fischbein NJ *et al.*, 1996[10]	Midbrain Diffuse Focal Tectal Pons Diffuse Focal Medulla Diffuse Focal Dorsal exophytic	MRI
Rubin *et al.*, 1998[11]	Cervicomedullary Exophytic Cystic Focal Diffuse	Clinical features and MRI
Choux M *et al.*, 2000[12]	Type I – Diffuse Type II – Intrinsic, focal Type III – Exophytic, focal Type IV – Cervicomedullary	CT and MRI

CT: Computerized tomography; MRI: Magnetic resonance imaging

of hydrocephalus or hemorrhage. The most recent and clinically used classification system was proposed by Choux *et al.* They classified brainstem tumors into four types by utilizing both CT and MRI images to group

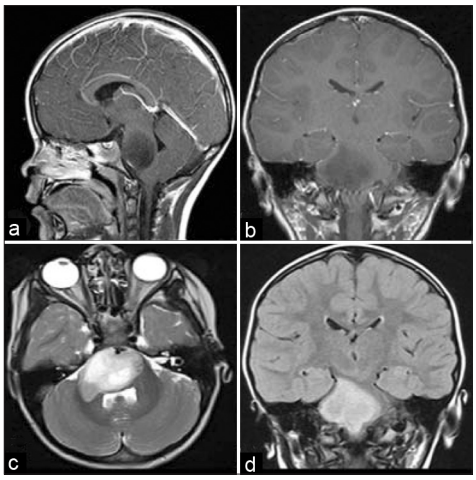

Figure 1: Diffuse brainstem glioma. This malignant tumor typically arises in the pons and causes global brainstem enlargement. Due to its infiltrative nature, it has poorly demarcated borders. On T1-weighted sequences, it is hypointense and does not significantly enhance with contrast (a and b). On T2-weighted (c) and FLAIR (d) sequences, it has indiscrete areas of hyperintense signal, which distinguishes them from focal tumors

them.[25] Type I are *diffuse brainstem gliomas*, which account for up to 75% of all tumors.[11,19] They are characterized by diffuse infiltration, global enlargement of the brainstem, and are generally greater than 2 cm at the time of presentation. The epicenter of the lesion usually lies in the pons with rostral and caudal extension not being unusual. On MRI, they are hypointense on T1-weighted images with variable contrast enhancement and have indiscrete hyperintensity on T2-weighted images[18] [Figure 1]. Typically, these lesions are located in the pons and are malignant fibrillary astrocytomas (WHO Grade III or IV). Type II are *focal*, intrinsic tumors that can be cystic or solid. Unlike Type I lesions, these tumors are sharply demarcated from surrounding tissue on MRI sequences and are associated with less brainstem edema. The majority of these lesions are low-grade gliomas (WHO I or II). Contrast enhancement may be variable, but uniform enhancement is highly suggestive of WHO I lesions.[9] Type III are *exophytic* tumors that arise from the subependymal glial tissue of the fourth ventricle and mostly grow dorsally or laterally. Radiographically, they possess MRI characteristics similar to type II lesions, and histologically, these lesions are usually low-grade lesions (WHO I or II). Interestingly, some authors have noted that exophytic tumors that grow laterally and ventrally into the brainstem are higher-grade lesions compared to those that project dorsally[24] [Figure 2]. Type IV lesions are *cervicomedullary* tumors similar in imaging, histology, and behavior to intramedullary spinal cord gliomas. The majority of type IV lesions are low grade, non-infiltrative, and thus their growth is usually confined rostrally by the white matter of the corticospinal tract and medial lemniscus[24] [Figure 3].

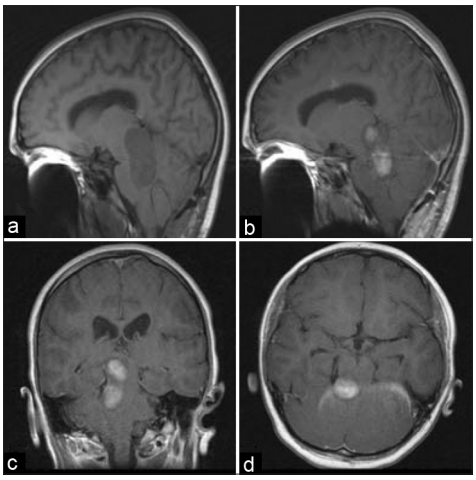

Figure 2: Dorsal exophytic tumor. This tumor is arising through the floor of the fourth ventricle. On T1-weighted sequences (a), these tumors are hypointense with variable patterns of contrast enhancement (b), which is suggestive of a low-grade lesion. On T2-weighted (c) and FLAIR (d) sequences, they are hyperintense with discrete borders, which further differentiate them from high-grade tumors. Histopathology revealed a juvenile pilocytic astrocytoma

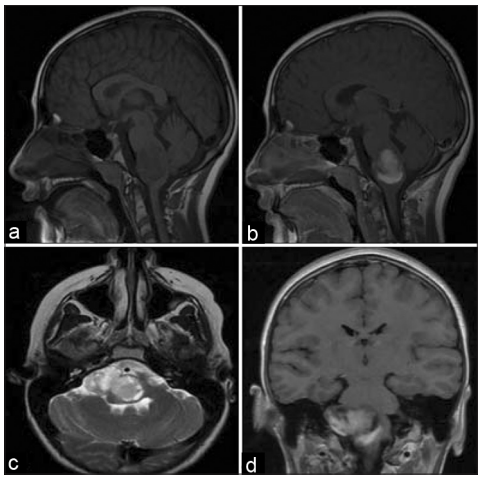

Figure 3: Focal medullary tumor. This tumor is hypointense on T1-weighted sequences (a), enhances strongly with contrast (b), and has sharply demarcated borders on T2-weighted and FLAIR sequences suggesting a low-grade tumor. In addition, crossing fibers at the pontomedullary and cervicomedullary junction are inhibiting further growth in the rostrol-caudal axis and causing the tumor to herniate into the cerebellopontine angle (c and d), which is consistent with a non-infiltrative lesion. Histopathology revealed a juvenile pilocytic astrocytoma

Management

Diffuse gliomas are extremely malignant lesions with a rapidly progressive course and dismal prognosis. The clinical course is similar to glioblastoma multiforme with no role for radical surgery. The diagnosis is generally made on imaging alone as biopsy carries unnecessary risk of morbidity and does not change management in most cases.[6,23,26] Stereotactic biopsy is reserved for indeterminate lesions on MRI with unusual presentations or when required by an investigational study protocol.[24] Medically, corticosteroids can be used to decrease the associated edema, although this effect is temporary. Conventional fractionated radiation has been shown to provide temporary stabilization or transient improvement of clinical symptoms.[8] Despite theoretical advantages, hyperfractionated radiation did not demonstrate any benefit over conventional radiation therapy for the treatment of diffuse brainstem gliomas in a large Phase III study.[27]

The primary treatment for focal tumors (Type II-IV) is surgical resection. The goal of surgery is to resect as much tumor as possible while avoiding neurological sequelae. Due to the lack of redundancy in the brainstem, surgical morbidity is significantly higher than other areas of the central nervous system.[8,24,28] Use of neurophysiological mapping and monitoring is essential to identify and avoid injury to vital brainstem structures.[29-32] Although radical resection can be safely achieved in selected cases, overly aggressive resection at the cost of permanent neurological deficit should be avoided.[24]

With the exception of upper midbrain neoplasms, tumors in the brainstem are accessed through a standard posterior fossa approach. The prone position provides easy access to the lower brainstem and allows manipulation of the patient's head and shoulders to maximize visualization. Some authors have advocated the sitting position, although this position carries risk of air embolism and pneumocephalus.[24,33] Focal intrinsic tumors which are dorsally located are commonly approached via a midline suboccipital craniotomy, while those in the ventral pons or those extending into the cerebellopontine angle exposed using a lateral retrosigmoid approach. The surgical approach into the medulla should provide wide exposure with identification of all crucial landmarks at the point of entry into the tumor.[28,34] Dorsal exophytic tumors are approached via a midline suboccipital craniotomy and a high cervical laminectomy, fourth ventricle exposure via a telovelar route avoiding vermian or cerebellar tonsil injury. As these tumors originate from ependymal cells on the floor of the fourth ventricle,[35] mapping of cranial nerve nuclei can be instrumental to avoid damaging them. If the tumor involves cranial nerve nuclei or motor tracts, radical resection should not be pursued. Although hydrocephalus secondary to tumor progression may develop after subtotal resection, management of hydrocephalus is preferable to incurring a risk of permanent cranial nerve deficits.[11,24,35,36] Focal medullary tumors typically bulge into the obex.[28,35] The approach is usually midline subocciptial craniectomy with cervical laminectomy. Intraoperative ultrasonography is used to delineate the tumor margins.[35,37] After the dura is opened, a midline myelotomy is performed to expose

the tumor and avoid damage to the posterior columns.[35] Aggressive radical excision of these tumors is ideal though subtotal debulking is also beneficial if a risk of damage to medullary structures is perceived.[10] In the case of intrinsic cervicomedullary tumors, resection of greater than 50% has shown to decrease tumor progression and increase long-term survival.[36,38-40] The high risks associated with radical resection should be kept in mind, which include damage to lower cranial nerves resulting in tracheostomy, feeding gastrostomy, voice changes, and increased incidence of upper respiratory infections and pneumonias.[38,41,42] Continuous neurophysiological monitoring during the procedure is indispensable to guide dissection around critical structures.[30,32,37]

The location of the tumor and type of treatment dictate the monitoring and postoperative management. Patients treated with CSF diversion for focal midbrain tumors have good outcomes[43] whereas open surgical excision can result in temperature control and sleep-cycle disturbances.[12] For those patients who have undergone prior shunt surgery, they should be monitored for reemergence of signs and symptoms of hydrocephalus and followed for potential shunt infection and failure.

POSTOPERATIVE COURSE

Diffuse brainstem gliomas, which are typically found in the pons, carry the worst prognosis. Survival rates at one year range from 35 to 46% and at three years range from 11 to 17%[18,44] following radiation therapy. Dorsal exophytic tumors treated with surgery have an excellent prognosis with Pollack *et al.* reporting a long-term survival of 94% in their series of 18 patients who underwent subtotal resections, with the one death related to a shunt malfunction. They also reported completed disappearance or stable residual disease in 11 patients.[36] Sixth and seventh nerve palsies are not uncommon as the nuclei are located in the floor of the fourth ventricle and can easily be damaged,[35] Hydrocephalus requires close observation and is treated with CSF diversion, if necessary.[35,36] Focal medullary tumors also have a long overall survival and progression-free survival after surgery and/or adjuvant therapy.[34,38] However, significant lower cranial nerve dysfunction has been reported in patients presenting with a history of voice changes, pneumonia, and upper respiratory infections with a higher risk of requiring postoperative ventilation,[39] In a series of 41 patients reported by Jallo *et al.*, 19 patients (46%) had significant lower cranial nerve deficits that required a tracheostomy, postoperative ventilation, and a feeding gastrostomy with a majority (79%) demonstrating significant resolution of their deficits.[41] In the case of cervicomedullary neoplasms, outcome after resection is directly related to the duration of the prodrome and the degree of preoperative dysfunction.[10,45]

FUTURE DIRECTIONS

Radiation and/or chemotherapy are the current mainstay for diffuse brainstem gliomas[46] neither providing a cure nor prolonging survival. Chemotherapeutic agents have minimal access due to blood brain barrier (BBB) obstruction to systemically administered drugs. The transient response to radiotherapy is brief and progressive symptoms can be expected at a median of about nine months after diagnosis. Delayed toxicity also includes the potential radiation necrosis of the brainstem and radiation-induced injury to the occipital lobes and the hypothalamic axis.[47,48]

Convection enhanced delivery (CED) is a method of local delivery that drives an infusate through the extracellular fluid in neural tissue by the use of a continuous pressure gradient.[49] Experimental studies have shown that CED can achieve a local drug concentration 10,000-fold greater than that achieved by intravenous drug administration without causing significant systemic exposure.[50,51] Another method of local drug delivery in set aliquots rather than a continuous infusion as in CED includes the use of a cannulated screw attached to the skull of the animal.[52,53] Although local delivery techniques have not yet transitioned to clinical use in humans, alternative devices and delivery methods may help attain a critical advantage in the fight against these tumors.

Brainstem tumors may also benefit from gene therapy with prodrug activation systems using the herpes simplex virus thymidine kinase (HSV-TK) gene and treatment with ganciclovir (GCV) for gene therapy.[54,55] HSV-TK converts the prodrug ganciclovir (GCV) into a toxic nucleotide analogue, whose incorporation into cellular DNA blocks cell proliferation. Following repetitive ganciclovir (GCV) intraperitoneal or intravenous injection, effective killing of glioma cells is observed.[56] Local production of endogenous inhibitors of angiogenesis (angiostatin, endostatin, and interferon (IFN)-alpha(1)) has been shown to decrease tumor size when transfected rat and human glioblastoma cells are implanted intracerebrally and release such factors.[57] Apoptosis-related genes, such as p53, have been demonstrated to slow tumor cell growth when transduced using adenovirus vectors.[58] Finally, chemo- or radio-sensitizing genes, which manipulate the cell cycle, have been shown to prolong survival in animals when successfully transduced in the presence of chemotherapy or radiation.[59,60] Genetic analysis of

such tumors now lies at the forefront of such progress as recent advances in DNA sequencing technology now provide the opportunity to survey mutational changes in cancer in a comprehensive manner, providing additional cellular targets for future gene therapy.[61]

CONCLUSION

Brainstem tumors are heterogeneous group of neoplasms that are treated based on their location and imaging characteristics. Diffuse pontine gliomas comprise the majority of brainstem tumors, respond poorly to surgery, and carry a poor prognosis. Focal brainstem tumors are less common but are amenable to surgical resection with good overall prognosis. Future treatments of diffuse and infiltrative brainstem tumors will depend on an increased understanding of their genetic makeup and the success of drug delivery therapies.

REFERENCES

1. Zhang C, Yao Y, Wang Y, Chen Z, Wu J, Mao Y, *et al*. Temozolomide for adult brain stem glioblastoma: Case report of a long-term survivor. Int J Neurosci 2010;120:787-91.
2. Guy G, Jan M, Guegan Y, Aubin ML, Fischer C, Ben-Hassel M, *et al*. [Surgical lesions of the brain stem]. Neurochirurgie 1989;35 Suppl 1:1-133.
3. Allen J. Brain stem glioma. Neurol Neurosurg Update Series 1983;4:2-7.
4. Walker DA, Punt JA, Sokal M. Clinical management of brainstem glioma. Arch Dis Child 1999;80:558-64.
5. Berger MS, Edwards MS, LaMasters D, Davis RL, Wilson CB. Pediatric brain stem tumors: Radiographic, pathological, and clinical correlations. Neurosurgery 1983;12:298-302.
6. Littman P, Jarrett P, Bilaniuk LT, Rorke LB, Zimmerman RA, Bruce DA, *et al*. Pediatric brain stem gliomas. Cancer 1980;45:2787-2.
7. Fulton DS, Levin VA, Wara WM, Edwards MS, Wilson CB. Chemotherapy of pediatric brain-stem tumors. J Neurosurg 1981;54:721-5.
8. Albright AL, Pollack IF. Brainstem gliomas. In: Winn HR, editor. Youmans Neurological Surgery. Vol. 3. 5th ed. Philadelphia: Saunders; 2004. p. 3663-9.
9. Recinos PF, Sciubba DM, Jallo GI. Brainstem tumors: Where are we today? Pediatr Neurosurg 2007;43:192-201.
10. Weiner HL, Freed D, Woo HH, Rezai AR, Kim R, Epstein FJ. Intra-axial tumors of the cervicomedullary junction: Surgical results and long-term outcome. Pediatr Neurosurg 1997;27:12-8.
11. Epstein F, Wisoff JH. Intrinsic brainstem tumors in childhood: Surgical indications. J Neurooncol 1988;6:309-17.
12. Hoffman HJ, Becker L, Craven MA. A clinically and pathologically distinct group of benign brain stem gliomas. Neurosurgery 1980;7:243-8.
13. Stroink AR, Hoffman HJ, Hendrick EB, Humphreys RP, Davidson G. Transependymal benign dorsally exophytic brain stem gliomas in childhood: Diagnosis and treatment recommendations. Neurosurgery 1987;20:439-44.
14. Alvisi C, Cerisoli M, Maccheroni ME. Long-term results of surgically treated brainstem gliomas. Acta Neurochir (Wien) 1985;76:12-7.
15. Epstein F, McCleary EL. Intrinsic brain-stem tumors of childhood: Surgical indications. J Neurosurg 1986;64:11-5.
16. Epstein F. A staging system for brain stem gliomas. Cancer 1985;56(7 Suppl):1804-6.
17. Barkovich AJ, Krischer J, Kun LE, Packer R, Zimmerman RA, Freeman CR, *et al*. Brain stem gliomas: A classification system based on magnetic resonance imaging. Pediatr Neurosurg 1990;16:73-83.
18. Fischbein NJ, Prados MD, Wara W, Russo C, Edwards MS, Barkovich AJ. Radiologic classification of brain stem tumors: Correlation of magnetic resonance imaging appearance with clinical outcome. Pediatr Neurosurg 1996;24:9-23.
19. Albright AL. Brain stem gliomas. In: J Y, editor. Neurological Surgery. Philadelphia: Saunders; 1996. p. 2603-11.
20. Dechambre S, Duprez T, Lecouvet F, Raftopoulos C, Gosnard G. Diffusion-weighted MRI postoperative assessment of an epidermoid tumour in the cerebellopontine angle. Neuroradiology 1999;41:829-31.
21. Murakami N, Matsushima T, Kuba H, Ikezaki K, Morioka T, Mihara F, *et al*. Combining steady-state constructive interference and diffusion-weighted magnetic resonance imaging in the surgical treatment of epidermoid tumors. Neurosurg Rev 1999;22:159-62.
22. Recinos PF, Roonprapunt C, Jallo GI. Intrinsic brainstem epidermoid cyst. Case report and review of the literature. J Neurosurg 2006;104(4 Suppl):285-9.
23. Albright AL, Packer RJ, Zimmerman R, Rorke LB, Boyett J, Hammond GD. Magnetic resonance scans should replace biopsies for the diagnosis of diffuse brain stem gliomas: A report from the Children's Cancer Group. Neurosurgery 1993;33:1026-29; discussion 1029-1030.
24. Jallo GI, Biser-Rohrbaugh A, Freed D. Brainstem gliomas. Childs Nerv Syst 2004;20:143-53.
25. Choux M, Lena G, Do L. Brainstem tumors. In: Choux M, Di Rocco C, Hockley A, editors. Pediatric Neurosurgery. New York: Churchill Livingstone; 2000. p. 471-91.
26. Albright AL, Guthkelch AN, Packer RJ, Price RA, Rourke LB. Prognostic factors in pediatric brain-stem gliomas. J Neurosurg 1986;65:751-5.
27. Mandell LR, Kadota R, Freeman C, Douglass EC, Fontanesi J, Cohen ME, *et al*. There is no role for hyperfractionated radiotherapy in the management of children with newly diagnosed diffuse intrinsic brainstem tumors: Results of a Pediatric Oncology Group phase III trial comparing conventional vs. hyperfractionated radiotherapy. Int J Radiat Oncol Biol Phys Mar 1999;43:959-64.
28. Epstein FJ, Farmer JP. Brain-stem glioma growth patterns. J Neurosurg 1993;78:408-12.
29. Morota N, Deletis V. The importance of brainstem mapping in brainstem surgical anatomy before the fourth ventricle and implication for intraoperative neurophysiological mapping. Acta Neurochir (Wien) 2005;148:499-509.
30. Morota N, Deletis V, Lee M, Epstein FJ. Functional anatomic relationship between brain-stem tumors and cranial motor nuclei. Neurosurgery 1996;39:787-93; discussion 793-784.
31. Morota N, Deletis V, Epstein FJ, Kofler M, Abbott R, Lee M, *et al*. Brain stem mapping: Neurophysiological localization of motor nuclei on the floor of the fourth ventricle. Neurosurgery 1995;37:922-9; discussion 929-30.
32. Sala F, Krzan MJ, Deletis V. Intraoperative neurophysiological monitoring in pediatric neurosurgery: Why, when, how? Childs Nerv Syst 2002;18:264-87.
33. Bricolo A. Surgical management of intrinsic brain stem gliomas. Oper Tech Neurosurg 2000;3:137-54.
34. Abbott R. Tumors of the medulla. Neurosurg Clin N Am 1993;4:519-27.
35. Jallo GI, Kothbauer KF, Epstein FJ. Surgical Management of Cervicomedullary and Dorsally Exophytic Brain Stem Tumors. Oper Tech Neurosurg 2000;3:131-6.
36. Pollack IF, Hoffman HJ, Humphreys RP, Becker L. The long-term outcome after surgical treatment of dorsally exophytic brain-stem gliomas. J Neurosurg 1993;78:859-63.
37. Epstein F, Wisoff J. Intra-axial tumors of the cervicomedullary junction. J Neurosurg 1987;67:483-7.
38. Abbott R, Shiminski-Maher T, Epstein FJ. Intrinsic tumors of the medulla: Predicting outcome after surgery. Pediatr Neurosurg 1996;25:41-4.
39. Abbott R, Shiminski-Maher T, Wisoff JH, Epstein FJ. Intrinsic tumors of the medulla: Surgical complications. Pediatr Neurosurg 1991;17:239-44.
40. Shiminski-Maher T. Brainstem tumors in childhood: Preparing patients and families for long- and short-term care. Pediatr Neurosurg 1996;24:267-71.

41. Jallo GI, Shiminski-Maher T, Velazquez L, Abbott R, Wisoff J, Epstein F. Recovery of lower cranial nerve function after surgery for medullary brainstem tumors. Neurosurgery 2005;56:74-7; discussion 78.
42. Shiminski-Maher T, Abbott R, Wisoff JH, Epstein FJ. Current trends in the management of brainstem tumors in childhood. J Neurosci Nurs 1991;23:356-62.
43. Li KW, Roonprapunt C, Lawson HC, Abbott IR, Wisoff J, Epstein F, *et al*. Endoscopic third ventriculostomy for hydrocephalus associated with tectal gliomas. Neurosurg Focus 2005;18:E2.
44. Packer RJ, Boyett JM, Zimmerman RA, Albright AL, Kaplan AM, Rorke LB, *et al*. Outcome of children with brain stem gliomas after treatment with 7800 cGy of hyperfractionated radiotherapy. A Childrens Cancer Group Phase I/II Trial. Cancer 1994;74:1827-34.
45. Robertson PL, Allen JC, Abbott IR, Miller DC, Fidel J, Epstein FJ. Cervicomedullary tumors in children: A distinct subset of brainstem gliomas. Neurology 1994;44:1798-803.
46. Allen JC, Siffert J. Contemporary chemotherapy issues for children with brainstem gliomas. Pediatr Neurosurg 1996;24:98-102.
47. Nelson MD Jr, Soni D, Baram TZ. Necrosis in pontine gliomas: Radiation induced or natural history? Radiology 1994;191:279-82.
48. Packer RJ, Zimmerman RA, Kaplan A, Wara WM, Rorke LB, Selch M, *et al*. Early cystic/necrotic changes after hyperfractionated radiation therapy in children with brain stem gliomas. Data from the Childrens Cancer Group. Cancer 1993;71:2666-74.
49. Bobo RH, Laske DW, Akbasak A, Morrison PF, Dedrick RL, Oldfield EH. Convection-enhanced delivery of macromolecules in the brain. Proc Natl Acad Sci U S A 1994;91:2076-80.
50. Groothuis DR, Ward S, Itskovich AC, Dobrescu C, Allen CV, Dills C, *et al*. Comparison of 14C-sucrose delivery to the brain by intravenous, intraventricular, and convection-enhanced intracerebral infusion. J Neurosurg 1999;90:321-31.
51. Occhiogrosso G, Edgar MA, Sandberg DI, Souweidane MM. Prolonged convection-enhanced delivery into the rat brainstem. Neurosurgery 2003;52:388-94.
52. Lee J, Jallo GI, Guarnieri M, Carson BS Sr, Penno MB. A novel brainstem tumor model: Guide screw technology with functional, radiological, and histopathological characterization. Neurosurg Focus 2005;18:E11.
53. Frazier JL, Lee J, Thomale UW, Noggle JC, Cohen KJ, Jallo GI. Treatment of diffuse intrinsic brainstem gliomas: Failed approaches and future strategies. J Neurosurg Pediatr 2009;3:259-69.
54. Miura F, Moriuchi S, Maeda M, Sano A, Maruno M, Tsanaclis AM, *et al*. Sustained release of low-dose ganciclovir from a silicone formulation prolonged the survival of rats with gliosarcomas under herpes simplex virus thymidine kinase suicide gene therapy. Gene Ther 2002;9:1653-8.
55. Burrows FJ, Gore M, Smiley WR, Kanemitsu MY, Jolly DJ, Read SB, *et al*. Purified herpes simplex virus thymidine kinase retroviral particles: III. Characterization of bystander killing mechanisms in transfected tumor cells. Cancer Gene Ther 2002;9:87-95.
56. Todo T, Rabkin SD, Martuza RL. Evaluation of ganciclovir-mediated enhancement of the antitumoral effect in oncolytic, multimutated herpes simplex virus type 1 (G207) therapy of brain tumors. Cancer Gene Ther 2000;7:939-46.
57. De Bouard S, Guillamo JS, Christov C, Lefévre N, Brugières P, Gola E, *et al*. Antiangiogenic therapy against experimental glioblastoma using genetically engineered cells producing interferon-alpha, angiostatin, or endostatin. Hum Gene Ther 2003;14:883-95.
58. Ruan S, Okcu MF, Pong RC, Andreeff M, Levin V, Hsieh JT, *et al*. Attenuation of WAF1/Cip1 expression by an antisense adenovirus expression vector sensitizes glioblastoma cells to apoptosis induced by chemotherapeutic agents 1,3-bis(2-chloroethyl)-1-nitrosourea and cisplatin. Clin Cancer Res 1999;5:197-202.
59. Miller CR, Williams CR, Buchsbaum DJ, Gillespie GY. Intratumoral 5-fluorouracil produced by cytosine deaminase/5-fluorocytosine gene therapy is effective for experimental human glioblastomas. Cancer Res 2002;62:773-80.
60. Yamanaka R, Yajima N, Tsuchiya N, Honma J, Tanaka R, Ramsey J, *et al*. Administration of interleukin-12 and -18 enhancing the antitumor immunity of genetically modified dendritic cells that had been pulsed with Semliki forest virus-mediated tumor complementary DNA. J Neurosurg 2002;97:1184-90.
61. Rand V, Huang J, Stockwell T, Ferriera S, Buzko O, Levy S, *et al*. Sequence survey of receptor tyrosine kinases reveals mutations in glioblastomas. Proc Natl Acad Sci U S A 2005;102:14344-9.

How to cite this article: Recinos PF, Rahmathulla G, Jallo GI, Recinos VR. Brainstem tumors: Current management and future directions. Indian J Neurosurg 2012;1:48-53.
Source of Support: Nil, **Conflict of Interest:** None declared.