Review Articles

Focal brainstem gliomas

Advances in intra-operative management

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ABSTRACT

أنظمة الملاحة العصبية المتطورة وكذلك التصوير أثناء العملية وتكنولوجيا الرصد الفيزيولوجية العصبية عززت من قدرة جراح المخ والأعصاب من استئصال أورام جذع الدماغ البؤرية، وفي المقابل تعتبر أورام جذع الدماغ المنتشرة غير قابلة للجراحة. هذه الورقة العلمية استمراراً لدراسة نشرت سابقاً لنفس الباحثين، ناقشت تشخيص وتصنيف وأيضا تصوير أورام جذع الدماغ. في هذه المقالة يشرح المؤلفان طرق وأساليب جراحة أورام جذع الدماغ أنظمة الملاحة العصبية المتطورة وكذلك التصوير أثناء العملية وتكنولوجيا الرصد الفيزيولوجية العصبية هي معايير مساعدة لجعل هذا النوع من العمليات آمنة وأكثر دقة وأقرب لتحقيق الهدف من إجرائها.

Improved neuronavigation guidance as well as intraoperative imaging and neurophysiologic monitoring technologies have enhanced the ability of neurosurgeons to resect focal brainstem gliomas. In contrast, diffuse brainstem gliomas are considered to be inoperable lesions. This article is a continuation of an article that discussed brainstem glioma diagnostics, imaging, and classification. Here, we address open surgical treatment of and approaches to focal, dorsally exophytic, and cervicomedullary brainstem gliomas. Intraoperative neuronavigation, intraoperative neurophysiologic monitoring, as well as intraoperative imaging are discussed as adjunctive measures to help render these procedures safer, more acute, and closer to achieving surgical goals.

Neurosciences 2015; Vol. 20 (2): 98-106
doi: 10.17712/nsj.2015.2.20140621

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The choice of entry and access to any brainstem lesion is one of the most difficult surgical decisions. In general, surgery is only beneficial for focal, exophytic, or cervicomedullary tumors. The surgery should obtain enough tissue for histological analysis. Surgery is aimed at complete resection when this is judged to be safe on imaging before operation. If that is not feasible, then the objective is reduction of the tumor burden as much as safely possible. The success of the surgery is partly related to tumor biology.[1] Safe entry zones, such as the suprafacial or infrafacial triangles, have been described (**Figure 1**); intrinsic tumors of the brainstem may distort the normal anatomy, thus obscuring the usual landmarks.[2,3] In general, to avoid permanent injury to neural tissue, the approach should not be aggressive. The main aim of surgery is complete removal of the tumor, which can be achieved by optimizing exposure and choosing a less risky, therefore safer, approach.[1] It is critically important to understand not only the microsurgical anatomy, but also the function of the location of the brainstem in which the lesion lies. Motor-evoked potentials in addition to fourth ventricular floor mapping can also be used to provide feedback during the resection. This article is a continuation of an article by the same authors that discussed brainstem glioma diagnostics, imaging and classification.[4] This article will address the surgical approaches to brainstem tumors

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

as well as related neuronavigation, neurophysiologic monitoring and intra-operative imaging technologies that aid to facilitate these surgeries.

Neuronavigation. Over the past 2 decades, stereotactic guidance and more commonly now, frameless neuronavigation (**Figure 2A**, **Figure 3**) are being increasingly used by many neurosurgeons in brain tumor surgery especially in complex and intricate areas of the brain.[3,5] The main objective is to accurately locate lesions and help avoid important functional and vascular structures in the brain. In brainstem surgery, neuronavigation is helpful in locating the lesions especially if they are covered partly by normal brain and pushing brainstem nuclei. More so, localizing normal white matter tracts to ovoid them during surgery can be done using neuronavigation using pre-acquired diffusion tensor imaging and white matter tractography information (**Figure 2D**). This is of particular use when trying to outline lesions at their connection to the brainstem, especially considering white matter tracts are usually deformed or deviated by lesions from their normal anatomic positions.[6,7] The caveat that surgeons commonly face with neuronavigation is the phenomenon of brain-shift and deformation that occur with cerebrospinal fluid (CSF) loss and tumor resection and retraction. This can be overcome with the advent of intraoperative imaging such as ultrasound, intraoperative CT, or MRI.[7]

Intraoperative magnetic resonance imaging (iMRI). The iMRI is one of the most helpful recent advances in neurosurgery (**Figure 2A**). During brainstem tumor surgery, often the exact boundaries of the tumor are not clear, brainstem structures are too precious to attempt to resect until normal tissue is seen, especially in cases where tumor tissue is similar to normal brain that has reactive gliosis. In these cases, iMRI helps acquire new images to verify the extent of resection

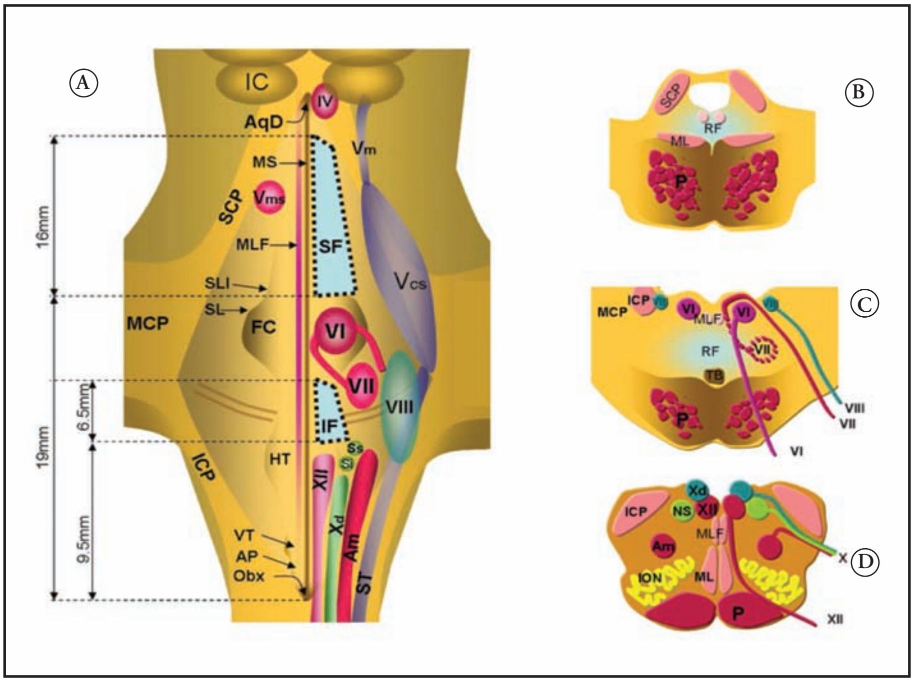

Figure 1 - *Illustration showing the **A**) dorsal view of the fourth ventricular floor. This illustration shows the supra-facial (SF) and infra-facial (IF) triangles. The column of illustrations on the right show corresponding axial sections through **B**) upper, **C**) mid, and **D**) lower pons. AqD - aqueduct of Sylvius, N - nucleus, IC - inferior colliculus, MS - median sulcus, Vm - mesencephalic N of the 5th cranial nerve (V), Vcs - chief (sensory) N of V, Vms - motor (mastication) N of V, MLF - medial longitudinal fascicle, FC - facial colliculus, IV - trochlear N, CTT - central tegmental tract, SL - sulcus limitans, SLI - sulcus limitans incisure, HT - hypoglossal triangle, SM - striae medullaris, SCP, MCP, SCP - superior, middle and inferior cerebellar peduncle, VT - vagal triangle, AP - area postrema, Obx - Obex, VI, Abducent N - VII, facial N. and fiber tracks and nerve, VIII - vestibular N. and nerve, XII - hypoglossal N. and nerve, Xd - dorsal vagal N, Am - N ambiguus of 9th and 10th cranial nerves with parasympathetics on its medial border, Ss & Si - superior and inferior salivatory NN., ST - spinal trigeminal tract, STT - spinothalamic tract, ML - medial lemniscus, ION - inferior olivary N., P - Pyramid, TB - trapezoid body, Pn TPF - pontine NN. and transverse pontine fibers, SF - Suprafacial triangle, IF - infrafacial triangle. **Figure 58.4 found on page 201 in Sabbagh AJ, Albanyan AA, Alyamany MA, Bunyan R, Abdelmoity AT, Soualmi LB. Case 58. In: Nader R, Sabbagh A, editors. Neurosurgery Case Review. NY (USA): Thieme; 2010 (reprinted with permission).*

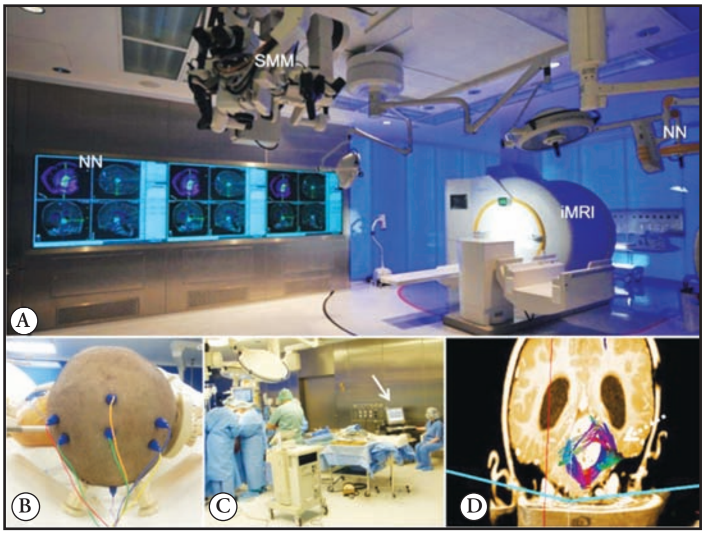

Figure 2 - Some of the available technologies **A**) intraoperative MRI suite where state of the art neuronavigation and intraoperative monitoring and imaging are performed at the National Neurosciences Institute, King Fahad Medical City, Riyadh, Saudi Arabia. **B**) patient's head in prone position connected through corkscrew iOM electrodes shown inside the MRI coil. **C**) Surgery starts after connecting the patient, iOM staff and equipment (arrow). **D**) Tractography imaging showing tracts displaced by tumor (dotted arrow). iMRI - intraoperative MRI device, NN - neuronavigation equipment and screen, ceiling mounted microscope, iOM - intraoperative neurophysiologic monitoring

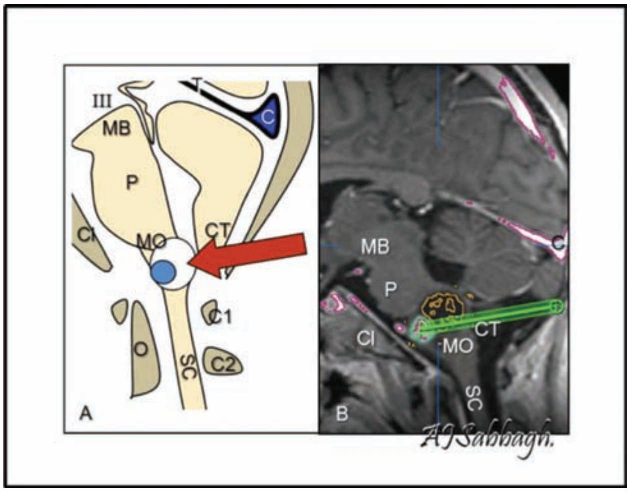

Figure 3 - Illustration depicting the posterior fossa, showing the trajectory to a medulla oblongata tumor (arrow) by artist rendering **A**) and neuronavigation screenshot **B**). The illustration shows the position of the neuronavigation probe (green rod), the third nerve (III), midbrain (MB), pons (P), medulla oblongata (MO), spinal cord (SC) clivus (CL), cerebellar tonsils (CT), odontoid process, tentorium (T), confluence of sinuses (C), cervical vertebrae one (C1), cervical vertebrae 2 (C2), odontoid (O)

and decide whether more surgery is needed.[8] As the anatomy changes during the surgery, combined iMRI and neuronavigation (**Figure 2A**) allowed safer resection in a study that included 127 patients.[9] Visualization of the tumor during the surgery results in more precise resection, and the outcome of surgery can be evaluated immediately.[10] This combination helps correct for brain shift during the surgical manipulation, and minimize neurological deficit post surgery.[11,12]

Intraoperative neurophysiologic monitoring (iOM). Surgery of the brainstem has significantly improved and been made relatively safer by advances in iOM (**Figures 2B & 2C**).[13] The iOM is classified into modalities that monitor the integrity of afferent and efferent long tracts passing through the brainstem, modalities that monitor the integrity of brainstem cranial nerve (CN) nuclei, and those that help locate CN nuclei through mapping in order to avoid them.[13-15] The objective of neurophysiologic testing is to reduce the risks inherent with the manipulation of the brainstem during surgery. Monitoring of the function of CN nuclei alerts the surgeon to any impending damage.[13-15] Intraoperative monitoring includes electroencephalography, CN-evoked potentials (EPs), brainstem auditory EPs (BAEPs), motor EPs (MEP), somatosensory EPs (SEP), nerve conduction, electromyography (EMG) signals, and brainstem mapping (BSM). Of the iOM techniques available, BSM and corticobulbar tract motor-evoked potential monitoring (CBT-MEP) are the most useful during brainstem glioma surgery.[16]

The BSM, also known as functional mapping or fourth ventricular floor mapping, can help localize CN nuclei prior to intervention, effectively creating a map for the surgical approach. It is usually applied immediately after the induction of anesthesia and the connection of EEG needles. The muscle sets commonly used for muscle activity recording during BSM are the orbicularis oris and orbicularis oculi for the VII cranial motor nucleus (CMN), the posterior pharyngeal wall for CMN IX/X, and the intrinsic tongue muscles for CMN XII. The cricothyroid or vocalis muscle can also be used for CMN X.[16] A monopolar probe is then used to stimulate the points of interest. After obtaining a muscle response, the stimulation intensity should be reduced to a threshold enabling precise localization of the CMN.[16-18] The BSM has been found to be effective in helping to avoid surgical damage to the CMN even when the usual landmarks are absent or distorted due to the presence of a brainstem glioma. The BSM, however, has several disadvantages including frequent interruption of the surgical procedure, the lack of representation of afferent fibers because it only covers the CMN and the efferent fibers, the limitation of its use to the dorsal brainstem and fourth ventricle, with limited use in ventral or lateral brainstem operations, and the fact that it only reflects a non-continuous, intermittent state of the brainstem.[16]

On the other hand, CBT-MEP provides continuous monitoring of the integrity of neural tissue throughout the neurosurgical intervention.[19] The scalp stimulation points are the same as those used in standard MEP monitoring, while the recording muscles are the same as those used for BSM. The CBT-MEP also requires the same preparation procedure as the BSM technique.[20] In contrast to BSM, CBT-MEP can be used in any surgery of the brainstem, including ventral or lateral operations. Another important advantage of CBT-MEP is that it can be used continuously throughout the surgery with no need to interrupt the surgical course.[16] The details of cortico-bulbar tract (CBT) anatomy are still not well defined, but Krieg et al and several other magnetic resonance based reports have investigated the anatomy and have documented promising results.[21,22] The CBT-MEP still lacks the ability to monitor sensory afferent fibers or the lower motor nuclei during surgery, which explains the dysphagia and dysarthria that can be found in patients despite exhibiting an entirely normal preserved CBT-MEP intraoperatively.[23]

The application of neurophysiological testing differs depending on surgical location (namely, midbrain, pons or medulla). For midbrain and pineal region tumors, BSM of the oculomotor and trochlear nuclei is helpful. Although a relatively new technique, CBT-MEP was found to be helpful with midbrain lesions, especially those approached by the subtemporal route.[23] Because they tend to displace the facial nucleus, pontine tumors should be monitored by the EMG response of the BSM, which was found to strongly correlate with postoperative functional preservation.[24] For medullary tumors, an initial BSM should be obtained before surgery but should also be repeated intermittently throughout the procedure, especially if it was not clearly located by the initial BSM. The interpretation of the BSM reading should be carefully assessed because the BSM may not indicate the functional preservation of afferent pathways, especially of the lower brainstem nuclei.[25] A combination of CBT-MEP and BSM, therefore, is important to help functional preservation of the brainstem during surgery.[14] Throughout the procedure, a collaborative and cooperative relationship between the surgeon, the neurophysiologist, and the anesthetist is critical. Neuroanesthesia during neuromonitoring consists of a total intravenous anesthesia infusion of a combination of Propofol and Fentanyl, with fine adjustment of Sevoflurane.[26]

The combination of intraoperative neurophysiologic monitoring and intraoperative MRI. The combination of intraoperative neuromonitoring with imaging is a novel technique only available in a few institutions.[27] The group in the National Neuroscience Center first reported resecting a brainstem glioma lesion using intraoperative high-field MRI with intraoperative neurophysiologic monitoring in 2009.[27] The combination is useful and is expected to help achieve even more accurate, safer brainstem tumor surgery with higher extent of resection.[26] One of the cautions one must be aware of is the need to use MRI compatible neurophysiologic monitoring electrodes, or they must be removed and replaced every time an MRI is to be performed; this may be somewhat difficult especially if patients are fully draped.

Awake craniotomy for brainstem glioma surgery. Although it may seem that awake craniotomy for brainstem glioma surgery would be ideal to detect and possibly prevent neurologic complications, positioning and the length of the surgical procedure makes this task very challenging. This may be utilized during a brainstem biopsy or for shorter debulking procedures (Del Maestro RF, Montreal Neurological Institute, Quebec, Canada, Personal communication, 2003 and 2014, oral communication).

Patient positioning and exposure of the brainstem. Almost all surgically accessible brainstem gliomas are dorsally located and, therefore, should be approached through the posterior fossa. In most cases, patients are placed in a prone position instead of sitting position (**Figure 2B**) for many reasons including to reduce the risk of venous air embolism.[28] A highly common practice is to position patients with a slightly flexed neck while applying anterior shoulder support. Another position that may be used for such tumors is the sitting position, this approach is associated with cerebral venous air embolism more commonly than the prone position, and may also be associated with surgeons arm fatigue, on the other hand, it provides more visibility and less need for retraction.[28-30] There is no evidence to suggest that the sitting position should be abandoned due to inherent risks. Choosing the correct approach must be based on neuroanatomical and functional data regarding tumor location and growth pattern in addition to surgical team's familiarity and experience with approaches and patient positions (**Figure 4**).[30]

Surgical approaches. In the following, surgical approaches will be discussed according to the location of brainstem tumors. Illustrations of some approaches are portrayed in **Figure 4**.

Midbrain gliomas. Almost all midbrain gliomas are focal, benign astrocytomas that arise from either the tegmentum or the tectal plate of the midbrain. Small, tectal tumors can be followed by serial MRI scans, while upper midbrain tumors in patients with hydrocephalus are usually treated with third ventriculostomy.[31,32] Some tumors, however, progress and require open surgery for reasons such as mass effect and neighboring anatomical structure compression.[32] Tumors in the tectal (dorsal mesencephalon) are primarily accessed by exposing the dorsal incisural space through a standard infratentorial supracerebellar approach (**Figure 4A**) first described by Krause and then popularized by Stein for tumors in the pineal region.[33,34] Tectal or tegmental tumors that are exophytic towards the aqueduct and the fourth ventricles can be reached through the subvermian approach, especially in cases where the fourth ventricle is dilated, (**Figure 4B**). The difficulty here is the need for significant neck flexion, and that may hinder venous return at the neck veins leading to more bleeding. Other pineal region approaches may be used such as the supratentorial occipital trans-tentorial approach (**Figure 4C**) depending on the location of the tumor and direction of growth onto the neighboring structures. Sufficient and safe exposure of the tectum is needed to prevent ocular and auditory functional damage as those are represented in the tectum. This can be obtained by placing a retractor that slightly displaces the superior-

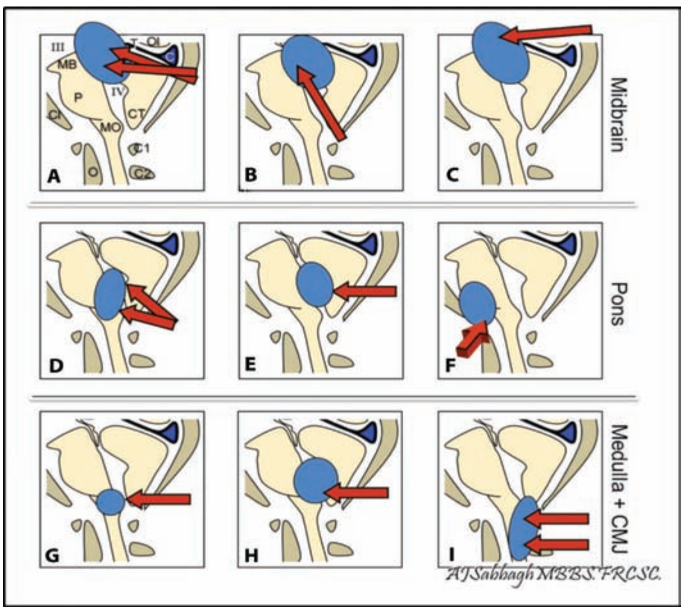

Figure 4 - Shows the diagrammatic illustration of some example approaches to the brainstem depending on region and location. Tectal region approaches (**A, B, and C**): **A**) supracerebellar-infratentorial, **B**) subvermial trans-forth ventricular, and **C**) occipital transtentorial approaches. Pontine region approaches (**D, E, and F**): **D**) telovelotonsillar, **E**) trans/subvermian, and **F**) transpetrosal (for anterolateral lesions) approaches. Cervico -medullary region approaches (**G, H, and I**): **G**) subvermian, **H**) Telovelotonsillar, and **I**) cervical approaches. The illustration shows the third nerve (III), midbrain (MB), pons (P), medulla oblongata (MO), spinal cord (SC) clivus (CL), cerebellar tonsils (CT), odontoid process, tentorium (T), and confluence of sinuses (C).

anterior surface of the cerebellum downwards after carefully dissecting the meninges.

Surgical access to median ventral surface gliomas is provided by a standard pterional transsylvian approach described by Yasargil et al[35] through a fairly safe, small rectangular area that spares the motor tract from the surgical field. For tumors involving the anterolateral aspect of the midbrain, the lateral mesencephalic sulcus is the safer entry zone.[36] However, a subtemporal transtentorial approach can be performed, which usually involves splitting of the tentorial incisura but risks injuring the vein of Labbé.[37]

Pons. The pons is the most challenging of all brainstem locations in terms of surgery. The postoperative complication risk is higher. Tumors located in the dorsal part of the pons and the upper medulla are accessed by a midline suboccipital craniotomy (**Figure 4D, 4E**) and a trans-fourth ventricle route as described by Bricolo and Turazzi.[38] Wide exposure of the rhomboid fossa and the fourth ventricle may be obtained. Exophytic tumors are exposed by elevating and splitting the cerebellar tonsils and vermis without excessive traction on the cerebellar hemispheres and avoiding dissection of the vermis. The posterior inferior cerebellar arteries are displaced laterally. Once the tela choroidea is exposed, it is cut at the taenia at both sides laterally and obliquely. Angulation of the surgical microscope then provides a complete view of the floor of the fourth ventricle.[39-41]

The peritrigeminal area is considered to be a safer entry zone when approaching anterolateral lesions of the pons.[36] Tumors that involve the ventral pons in the area of the cerebellopontine angle are accessed by the standard lateral retrosigmoid approach through a lateral suboccipital retromastoid craniectomy, similar to that used in acoustic neuroma surgery. Using the asterion formed by the lambdoid and temporal squamous sutures as a landmark for bony removal, the junction between the transverse and sigmoid sinuses is used as a guide for dural opening. The bulging pons is entered through the fissure between the stretched fifth, seventh, and eighth CNs, and the tumor is debulked with attention devoted to the tracts of CN V, CN VII, and CN VIII.[42,43]

Focal ventrolateral pontine tumors are very rare, and they may be reached through a combined petrosal approach (**Figure 4F**) which combines a subtemporal and a transtentorial presigmoid avenue, an approach that has the advantage of a short distance and a direct line of sight to the anterolateral brainstem.[44,45]

Medulla and cervicomedullary junction. The retro-olivary sulcus area is considered to be the safer entry zone to the medulla, with low midline suboccipital craniectomy and cervical laminotomy (**Figures 4G, 4H, 4I**) being the approaches currently used for medullary and cervicomedullary junction gliomas.[36] When these tumors are medial, it is best to access them through a midline longitudinal myelotomy.[46] A tumor that is more laterally or ventrally located is best accessed using the dorsolateral approach described by Spetzler and Grahm.[47] For tumors located in the ventral middle part of the medulla this access provides sufficient exposure of the anterolateral aspect of the medulla, the cervicomedullary junction, foramen of Luschka, CN IX through CN XII, and associated arteries. Intra-axial lesions that expand into the lower brainstem are approached through a restricted retrosigmoid craniotomy and C1-hemilaminectomy with drilling of the posterior third of the occipital condyle when necessary, and not exceeding the posterior third of the condyle to preserve stability. In addition, when resecting cervicomedullary gliomas, the posterior inferior cerebellar artery could be injured. Therefore, it is essential to identify it before resecting.

Exophytic tumors. Dorsally exophytic tumors are primarily localized to the floor of the fourth ventricle. One of the standard approaches is the midline suboccipital craniotomy (**Figure 4A**).[47] Most of the debulking occurs outside of the brainstem. The floor of the fourth ventricle should be exposed before debulking the tumor. It is possible to map the fourth ventricle during tumor resection. If there is distortion of the floor of the fourth ventricle by the tumor, ultrasound can be used to ascertain where the tumor is closest to the floor. CN 6 and CN 7 nuclei and/or tracks are susceptible to injury; this is where intraoperative neurophysiology plays an important role.[48] These exophytic tumors are exposed after the vermis is split. Cerebellar mutism and pseudobulbar symptoms can occur with excessive traction.[39] In addition, when resecting cervicomedullary gliomas, the posterior inferior cerebellar artery could be injured. The posterior inferior cerebellar arteries are laterally displaced. The goal is to shave the tumor to be flush with the surrounding floor of the ventricle and to not proceed ventrally in this plane unless the tumor is clearly differentiated from the normal brain tissue and neurophysiologic monitoring shows no changes. One must keep in mind to maintain good visualization of the ependyma above and below the tumor as well as and to avoid resection below the ependymal floor. However, because many of these lesions arise from the floor of the fourth ventricle, complete resection of the tumor may not be possible. Therefore, the majority of dorsally exophytic tumors can be managed successfully with subtotal resection and, if necessary, CSF diversion.[46,49]

If the lesion occupies the facial colliculus and points to the floor of the fourth ventricle, it can be accessed through the infrafacial triangle by the suboccipital craniotomy-vermis-sparing telovelar approach. This approach can be further evaluated by use of neuronavigation and microscopy.[50,51]

Postoperative care and possible complications. Patients are typically monitored for worsening signs and symptoms. One of the most common postoperative risks in the management of lesions involving the medulla is progressive carbon dioxide retention.[52] Respiratory collapse can occur within the first 48 hours after surgery, with associated injury to a portion of the medulla. Therefore, the patient should be very closely monitored in the intensive care unit or even left intubated for at least 48 to 72 hours after surgery. After 24 consecutive hours of stable respiratory drive, the patient is weaned from the ventilator. The oral or nasal tracheal tube is maintained with mechanical ventilation and necessary sedation. A CT scan is performed to rule out early bleeding, hydrocephalus, and pneumocephalus.[53] If the CT scan is normal, the tracheal tube may be safely removed when the patient achieves normal ventilation with normal cough and swallowing. Patients are given high dose steroids (for example 6 mg of Dexamethasone every 6 hours depending on their weight) for the first 3 days postoperatively and this is followed by a tapering dose depending on the clinical need.

In general if non-absorbable skin sutures are used they can be removed within 10 days of the surgery as long as there are no signs of CSF leak. Cranial nerve injuries are related to location of tumors, and the surgical approach as well as brainstem injury. Lower cranial nerve injuries are quite common in medullary brainstem surgery, around two thirds recover or significantly improve.[54] Most patients experience transient worsening of swallowing and difficulties that improve in the following weeks after the surgery, some do not improve.[55] Sudden post-operative death in the following weeks to months is reported.[56] Some patients remain with long term needs for tracheostomy and gastrostomy tubes because of swallowing difficulties and for airway protection, and this along with other mentioned possible complications must be addressed with patients and their guardians before surgery.

Other possible complications that are not uncommon include those that are associated with cerebellar and especially vermian surgery and traction such as mutism and behavioral changes[39] in around 10% of patients. Patients that have focal brainstem lesions and received preoperative radiation are at higher risk for developing perioperative and post-operative morbidities.[56]

Prognosis and postoperative expectations. Location of the lesion and whether it compresses or infiltrates the surrounding structures are, by far, the most important prognostic indicators for brainstem gliomas. Symptoms lasting more than 3 months were reported to be a favorable prognostic factor in a study involving 48 adults.[57] Generally around two-thirds of patients improve after surgery compared with the preoperative status according to Teo and Siu,[58] whereas 12% and 21% of patients that have low and high grade gliomas become worse consecutively after surgery. They also documented that all patients who had low grade gliomas were alive at 5 years compared with one third of those that harbored high-grade gliomas.[58] Patients that have pontine tumors are at a higher risk of developing surgical complications than those who have midbrain and cervicomedullary tumors.

Patients with diffuse infiltrating brainstem gliomas are generally not surgical candidates and have a much poorer outcome, with an overall survival rate of 5-20% at 2 years. Patients presenting with older age, absence of CN deficit and long tract symptoms, and longer duration of signs and symptoms are considered to have a better prognosis.[59] Intra-tumoral hemorrhage in patients with diffuse brainstem gliomas may complicate clinical management. Favorable prognostic factors include having the epicenter of the lesion within a non-pontine territory of the brainstem, a prolonged history, a focal positive neurological examination, uniformity of the signal within the tumor on imaging studies or as a flair high signal and calcification on CT. Similarly, a growth pattern limited to a segment, or when there is a deviation to the floor of the fourth ventricle, the presence of a cyst and having neurofibromatosis[1] are all considered good prognostic factors.[60-62] However, tumor necrosis and hydrocephalus on imaging had no prognostic significance.[63] Significant post-operative complications and neurologic deficits especially lower cranial nerves may negatively influence prognosis.

In conclusion, treatment of focal brainstem gliomas has significantly progressed as a result of the gradual advancements in microsurgical techniques, sophisticated pre and intraoperative imaging and neurophysiologic technologies; however, it still considered one of the most difficult tumors to treat.

Acknowledgment. *We would like to thank Dr. Lahbib Soualmi and Dr. M. Tariq Imtiaz for providing neuronavigation and monitoring information and images. We also would like to thank Dr. Ibrahim Alzahrani for providing the Arabic translation. In addition, we acknowledge Dr. Mahmoud Alyamany, Dr. Yasser Orz, Dr. Maqsood Ahmed, Dr. Ahmed Lary, Dr. Ayman Albanyan, Dr. Reem Bunyan and Dr. Lahbib Soualmi for being the first team internationally to combine intraoperative MRI with Neurophysiologic monitoring during neurosurgical cases around the end of 2007 at the National Neurosciences Institute, King Fahad Medical City. We also would like to thank the College of Medicine Research Center, Deanship of Scientific Research, King Saud University for supporting the study.*

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