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Systematic Review

Resection of Brainstem Metastases Malformation: Pearls and Pitfalls for Minimizing Complication

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Abstract

Introduction: Management of brainstem metastatic tumor is challenging. brainstem metastasis is an uncommon complication of systemic cancer, generally considered to have a highly unfavorable prognosis. Surgical risks are high and standard radiation or chemotherapy have little effect. The purpose of this study is to evaluate our experience an overview of the removal of abnormalities of brain stem metastases and the general treatment protocol of these types of metastases, which are very unfavorable.

Methods: The present paper is a literature review using the following databases: PubMed, Scientific Direct, Library Genesis, using the terms: Brainstem Metastases Malformation. Articles from May 2019 were selected, resulting in a total of 19 articles that met the inclusion criteria considering their citations and respective impacts.

Results: Complications were predicted and observed according to existing factors and factors that will arise in the future. Local tumor control was achieved in 90.7% of patients.

Conclusion: The results of this small series demonstrate that treatments now can be a valuable modality for safe and effective management of brain stem metastasis. Owing to the high risk of surgical resection and low efficacy of medical treatment, radiosurgery can be proposed upfront.

Keywords: Brainstem Metastatic, Radiosurgery, Systemic Cancer, Chemotherapy, Abnormalities

Introduction

The central nervous system is a remarkably beautiful, intricate, and delicate structure. In generally patients with brain metastases generally reserve a poor prognosis despite modern therapies.[29,30] Brain metastases are the most common intracranial neoplasm, with an annual incidence of nearly 170,000 to 200,000 cases diagnosed in the United States. Of these, only about 3-5% occur in the brainstem.[16,25,31] The prognosis of brainstem metastases is highly unfavorable with survival ranging from 1 to 6 months.[8]

The most common route of brain metastasis is hematogenous spread though perineural spread has also been documented.[17] Neurological deficiencies are the main symptoms caused by the growing tumor mass. The dense concentration of neural tracts and nuclei in the brainstem means that brainstem metastasis frequently causes significant neurological defects including cranial neuropathies and deficits of motor and sensory nerves. Although relatively uncommon, brainstem metastases come with a poor prognosis and estimated survival without treatment is one to six months.[18] Early detection and appropriate treatment of brain metastasis are crucial in minimizing the consequences of imminent disability. Brainstem metastases (BSMs), however, present a challenge to both patients and physicians, because they frequently cause significant neurologic compromise and are generally not amenable to surgical resection.[26]

Usually, the clinical presentation of brainstem CN often correlates with their anatomical location. Somatic motor and sensory symptoms predominate, as would be expected given the presence of these tracts along the entire axis of the brainstem.[4,5] Oculomotor abnormalities are more common with lesions of the mesencephalon compared with other portions of the brainstem.[5] Ataxia, meanwhile, has been reported more commonly with lesions situated toward the medulla although this is not always the case, as cerebellar long tracts and cerebellar peduncles are present in all segments of the brainstem.[5,6]

Anatomy of Brainstem

Although not an exhaustive treatise on brainstem anatomy, in this article, we provide a very simple summary for a better understanding of anatomy and Histopathology for brainstem. There are not completely “safe” entry zones to the brainstem, but knowledge of brainstem anatomy and how it relates to a particular lesion will help guide the surgeon to the best approach.

Nestled between the clivus and the cerebellum, the brainstem is a relatively small, yet highly inter-connected structure. Except for olfaction and vision, all sensory and motor pathways flow through the brainstem, making it a primary gateway between the mind and body.

Sensations related to the immediate environment (tactile, taste) might have been an early addition and are localized to the hindbrain. Distant sensations (vision, olfaction) emerged later; hence, they are located in the midbrain and forebrain. On the other hand, orientation in space (labyrinth) originated early along with motor coordination. Hearing later branched as an adaptation of the vestibular system and vibratory perception. Associative and correlative functions began to unfold in the midbrain (e.g., optic tectum), followed by the emergence of higher diencephalic centers.[1] Hence, the thalamus anatomically constitutes a rostral continuation of the midbrain with no sulcal separation between the two.

the underlying structures. The surgeon should be familiar with the anatomy surrounding the brainstem at each level. In every direction, except for the middle cerebellar peduncle and fourth ventricle, there is a subarachnoid cerebrospinal fluid (CSF) cistern immediately adjacent to the brainstem. Each of these typically contains vessels and one or more CNs (Figure 1).

Given the high concentration of eloquent structures in the brainstem, lesions are usually resected through their exophytic portion, if present. When the lesion does not present itself to the pial surface, anatomical entry zones[2,3] can be exploited to access it with the least possible risk of neural injury. Below is a list of the described zones, which are also summarized in Table 1.

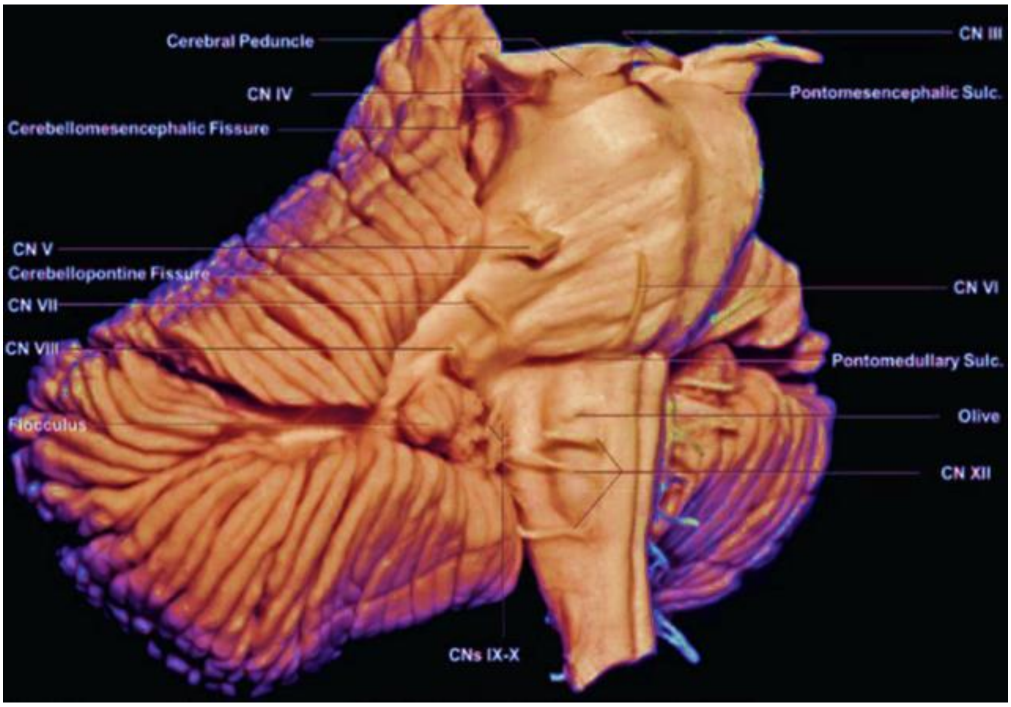

Figure 1. Brainstem seen from the Anterolateral Perspective. Sulc: Sulcus; CN: Cranial nerve.

Table 1. List of the Described Zones

Region	Safe Entry Zone (s)	Limits	Surgical Approach (s)
Midbrain			
Ventral	Perioculomotor zone	Pyramidal tract and exit of CN III	Pterional/FOZ-Transcavernous
Antero- lateral	Lateral mesencephalic sulcus	Cerebral peduncle and tectal area	Subtemporal Lateral infratentorial
Posterior	Supracollicular zone Infracollicular zone Intercollicular zone	Transverse line above the superior colliculi Transverse line below the inferior colliculi Vertical line between colliculi	SCIT Occipital trans-tentorial
Pons			
Antero-lateral	Peritrigeminal zone Area lateral to CNs V-VII; MCP	Vertical line on the medial aspect of CNs V and VII entry points, lateral to pyramidal tract Lateral to entry points of CNs V and VII	Retrosigmoid Transpetrosal approaches
Dorsal	Median sulcus Suprafacial collicular zone Infrafacial collicular zone	Midline between bilateral MLFs Above facial colliculus Facial colliculus and hypoglossal trigone	Transcerebellomedullary fissure telovelar Transvermian
Medulla			
Antero-lateral	Pre-olivary sulcus Retro-olivary sulcus	Olive and pyramidal tract Olive and ICP/CNs IX and X	Far lateral
Dorsal	Posterior median sulcus Posterior intermediate sulcus Posterior lateral sulcus	Bilateral gracile tubercles Gracile and cuneate tubercles Lateral to cuneate tubercle	Suboccipital

CN: Cranial nerve; FOZ: Fronto-orbito-zygomatic; ICP: Inferior cerebellar peduncle; MCP: Middle cerebellar peduncle; MLF: Medial longitudinal fasciculus; SCIT: Supracerebellar-infratentorial.

Pathology

In generally the brainstem contains all cell types of the central nervous system, that Consequently, the brainstem may be involved in infectious, oncologic, neurodegenerative, and vascular disease processes.

The brainstem that not only serves as a conduit for nearly all the information between the brain and the spinal cord and elsewhere, but also performs numerous vital functions by the presence of cranial nerve nuclei and centers of control for many essential functions. In generally even the smallest lesion may have profound effects on brainstem function. Histological standpoint, the brainstem contains all the cellular elements, including neurons, glia, leptomeninges, ventricular surfaces, and a rich vascular supply. For obvious reasons, much of the abnormal pathology of the brainstem cannot be easily assessed by large biopsies or resections and is therefore elucidated by neuroradiological studies and autopsy-based examinations.[43,44]

According to the anatomical position of the brain stem, it is composed of three parts, each of which includes a series of Developmental and Acquired Malformations.

Tumors of the brainstem include many among the primary neuroepithelial tumors, including astrocytoma's, glioneuronal tumors, and very rarely oligodendrogliomas. Given the tendency of childhood brain tumors to originate in the posterior fossa in general, it is important to distinguish between tumors that arise in the brainstem itself and those that originate in the cerebellum, cranial nerve tumors, and intraventricular tumors. Among these tumors, it is useful to subdivide those that typically arise in the midbrain, pons, or medulla.[45,46]

The available evidence indicates that there are no other injuries that have dangerous and harmful effects on the CNS, especially the brainstem, which can cause irritation of the existing risk factors for patients (Table).

Table 2. Rare Intrinsic Tumors of the Brainstem

Tumor	Brainstem Involvement
Hemangioblastoma, World Health Organization grade I	Medulla, sporadic
Primitive neuroectodermal tumor (Central nervous system embryonal tumor)	Pons
Metastatic	Most commonly from lung and breast primary tumors
Germ cell tumors, mostly germinomas	Diverse manifestations. Mostly favorable outcomes with chemotherapy and radiation therapy

Table 3. In the Extraordinary Table of Diseases and Diseases in the General CNS, Especially in the Brain Stem

Infections	
1.	Bacterial
2.	Viral
Inflammatory Diseases	
1.	Demyelinating Diseases
2.	Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids
3.	Bickerstaff's Brainstem Encephalitis
4.	Paraneoplastic Brainstem Encephalitis
Metabolic and Toxic Injury	
1.	Central Pontine Myelinolysis
2.	Multifocal Pontine Leukoencephalopathy
Vascular	
1.	Arteriovenous Malformations
2.	Cavernous Malformation
3.	Hypoxia-Ischemia
Trauma	
1.	Duret Hemorrhages
2.	Traumatic Axonal Injury
Neurodegenerative Diseases	
1.	Alzheimer disease (AD)
2.	Synucleinopathies
3.	Parkinson disease (PD)
4.	Dementia with Lewy bodies (DLB)
5.	Multiple system atrophy (MSA)
6.	Progressive supranuclear palsy
7.	Motor neuron diseases
8.	Bulbar hereditary motor neuropathies (progressive bulbar palsy)
9.	X-linked bulbospinal neuropathy (spinobulbar muscular atrophy, Kennedy disease)
10.	Spinal muscular atrophies
11.	Amyotrophic lateral sclerosis

Materials and Methods

Search Strategy for Identification of Studies

The purpose of searching the literature was to identify evidence of resection of brainstem metastases. The Medline, PubMed, Scientific Direct, Library Genesis database (from 1960 to 2019) and the Cochrane Library were searched for potentially relevant articles. The search strategy combines controlled vocabulary and textual terms for brainstem metastases and brain metastases. In addition, the bibliographies of all included reviews and included studies were searched for additional references, which were not registered in the above-mentioned databases. Experts in the field of Neurosurgeon and Neuro-oncologist Surgery were also asked to supply additional articles.

Selection of Articles

Articles were selected based on title and abstract. The following inclusion criteria were used: (i) brainstem metastases, (ii) the relationship between brainstem metastasis and applied treatments, (iii) histopathological, physio pathological and serological factors, brainstem metastasis, (iv) all articles with Examine different but effective languages on the subject. Each article must meet all four criteria. There were no restrictions on study design. The following two criteria were used to exclude articles: if only a comparison was made between experimental and non-experimental, or if a comparison was made between treatment and other relevant factors relative to the main variable. If the abstract was not available electronically or the article abstract information was insufficient, the articles were reviewed in full text for more detailed information. All retrieved articles were reviewed in full text by all authors to ensure that they met the inclusion criteria. In case of disagreement in the selection of articles between the two judges, the abstracts and articles were re-examined and discussed until a consensus was reached.

Results

A total of 19 studies met the inclusion criteria for the review.

Flow of Studies through the Review

The electronic search identified 188 articles. After screening all titles and abstracts, 19 articles were identified but after reviewing the full text, five of these were excluded from the review. The main reasons for exclusion was that the measurement tool involved a therapies were outside the main subject of the research or the expressions of the required variables were outside the scope of our subject. Systematic review and meta-analysis of the leaf balance scale were identified in the search, and its reference list was screened to identify additional items not found in the electronic search. When the reference lists of previously identified systematic reviews were reviewed, additional articles were identified and included in the review. Upon reviewing the reference lists and abstracts of potentially relevant papers no extra articles were found to be relevant.

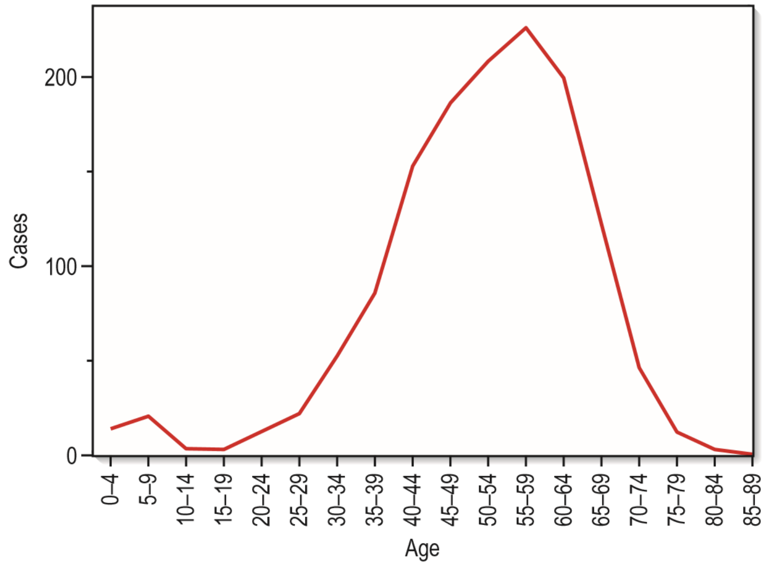

Figure 2. Histogram of the Incidence of Brain Metastasis based on Age[52]

Characteristics of Included Studies

The 19 included studies involved participants (some of the included studies reported data for the same participants, where this was the case the participant was counted only once). a variety of measurement tools captured. A summary of the studies is presented. An Effect Size was calculated in one study where data was available but an Effect Size was not included in the original article. Most of the included studies were prospective cohort studies. Limitations of studies include with less data volume were also considered in the main process of the workflow (Figure 3).

Discussion

This Review Literature summarized current studies relating to Brainstem Metastasis Malformation was due to the desired therapeutic and pathological events in this type of tumor. This review demonstrated the variability in the responsiveness of these measures. Given the favorable local control shown in the brainstem and the lack of data on the prognosis of brainstem metastases, we sought to determine whether metastatic disease in the brainstem affects survival after treatment compared to patients with brain metastases that involve the brainstem. It is not brain or not, we were.

The brainstem contains several densely packed, critical neural tracts. As a result, tumors that metastasize to the brainstem pose a difficult therapeutic challenge, and local progression can result in rapid neurologic decline or death. Resection of a brainstem metastasis is seldom performed given the operative risk, comorbidities, and overall prognosis of this patient cohort.[78]

The pineal region and thalamus are challenging to access because of their central location within the calvaria near important surrounding neurovascular structures. Likewise, lesions in the brainstem are challenging because of the many pathways and nuclei packed into a small area and the risks of exposing intra-axial brainstem pathology. However, improved imaging techniques, electrophysiological monitoring, and more precise microsurgical and endoscopic techniques have decreased morbidity and mortality rates related to surgery for brainstem, thalamus, and pineal region lesions (e.g., cavernous malformations and gliomas). These surgeries have also been facilitated by safe entry zones, and surgical approaches that can be tailored to the morphology.[32-39]

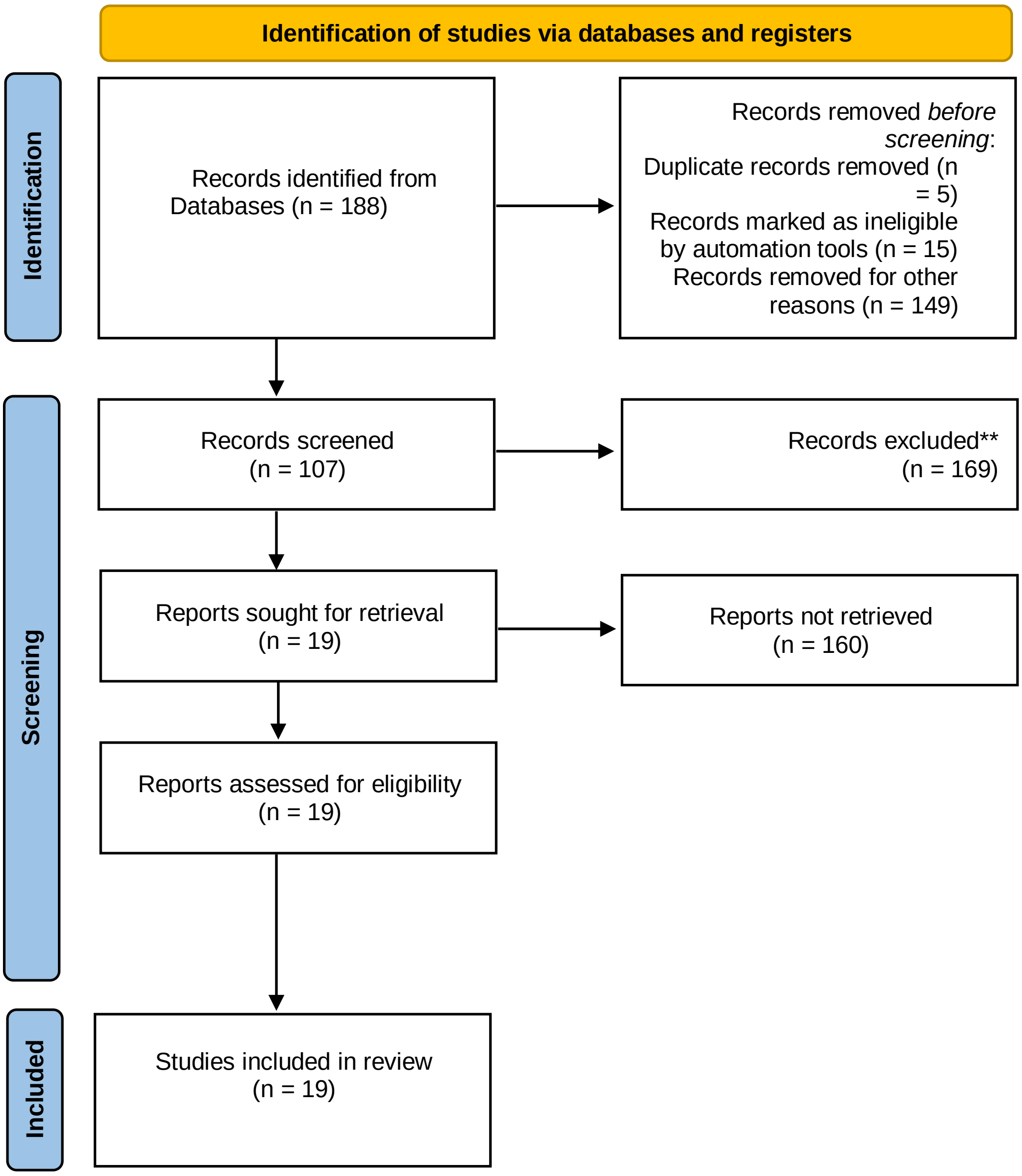

Figure 3. PRISMA Flow Diagram

Brainstem Metastases

Metastatic tumors within the brainstem pose many unique and difficult therapy decisions. Local progression of disease within the brainstem is associated with an acute and severe neurologic decline. Access by craniotomy is not indicated because of the risk associated with the approach corridors needed to respect the metastasis even if it is exophytic. Systemic chemotherapy has little demonstrated effectiveness.[62]

Tumors were said to be controlled locally if they were decreased or unchanged in size, and to have failed locally if they increased in size (as determined by a volume increase of >10%) over the follow-up period.[63]

Unlike other locations within the brain, brainstem metastases are seldom resected given the surgical risks associated with their location in regions of critical brain function.[64] The literature reports conflicting recommendations on resection of this abnormality of metastases to maximize the cure ratio.

Approximately, 80% of brain metastases occur in the cerebrum, another 10-15% in the cerebellum and about 2-3% in the brainstem.[65] Although brainstem metastases are rare, they are associated with the worst prognosis with a survival rate of 1-6 months without directed therapy.[66,67] Brainstem metastases (BSM) are often inoperable, compromised by the density of functional fiber tracts converging in a small cross-sectional area/volume.[66]

Brainstem metastases are a particularly difficult oncological and neurological clinical problem. In most cases, these lesions are inoperable and carry a grim prognosis.[68,69] Furthermore, most chemotherapeutic agents cannot pass through the blood brain barrier making chemotherapy ineffective. The presenting signs and symptoms of studies are shown in Table 4.

Table 4. Symptoms in Patients with Brainstem Metastasis (%)

Symptom	Study and Number of Patients
Headache	44 %
Focal weakness	18 %
Facial weakness, causing asymmetry or drooping of saliva	22 %
Seizure	19 %
Ataxia	6 %
Aphasia	1 %
Failure to thrive in young children	1 %
Sensory change	10 %

The unregulated cell cycles of cancerous cells in the brain have a faster turnover rate and a reduced ability to repair DNA damage. The prognosis for patients with brainstem metastasis is very poor with a median survival time ranging from 4 to 12 months.[68,70,71]

The chance for long-term survival at one year is approximately 30% according to a study done by Hussain et al.[72] Furthermore, a review of the literature reveals a current controversy over which treatment modality, or combination thereof, provides the best treatment and survival probability for the patient. In a report written by Aoyama et al.[73]

Brain metastases are hematogenous spread, and it is posited that the relatively low incidence of these lesions is linked to the fact that brainstem receives lower blood flow than other parts of the brain.[74] The prognosis for patients with brainstem metastases is poor. These lesions are rarely operable, and, in most cases, it is not possible to achieve local control with conventional radiotherapy options.[75]

Brainstem metastases are usually evaluated differently from metastases in other brain locations because of the lower radiation tolerance of brainstem tissue and its neurological importance.[76] These metastases are not easy to access surgically, and WBRT alone does not achieve sufficient local control in most cases.[77]

Surgical Approaches

Depending on the location of the lesion in the thalamus, the approach may be the anterior interhemispheric transcallosal approach (including the trans ventricular, transforaminal, and trans choroidal or transcortical variations), or the posterior interhemispheric transcallosal, parieto-occipital transcortical trans ventricular, or infratentorial sup acerebellar approach.[34,40]

Several different types of tumors can occupy the pineal region, including tumors originating in the pineal body (pine-aloblastomas/pineocytomas, teratomas, and germinomas), in the splenium of the corpus callosum (intrinsic glial tumors), in the velum interpositum (meningiomas), or in the fornix.[41,42]

The surgical approaches used to access lesions in the pineal region are dependent on the complex anatomical relationship of the surgical target to surrounding structures, the location of the arteries feeding the lesion, anatomical variations, and the extent of resection goals. A wide variety of approaches the morphology of the target lesion. These approaches include the infratentorial sup acerebellar approach, the posterior-interhemispheric trans tentorial approach, the occipital interhemispheric approach, the parieto-occipital interhemispheric transcallosal approach, the posterior transcortical approach via the angular gyrus and lateral ventricle, the posterior sub temporal approach, and the combined supra- and infratentorial trans sinus approaches

In generally these preliminary results provide evidence that the development of brainstem metastases is associated with inferior survival compared to patients with non-brainstem brain metastases, despite favorable local control in the modern treatment era. The results obtained could not show that extracranial disease or a specific histology is associated with brainstem metastasis.[79-81]

Conclusion

The importance of knowledge by neurosurgeons and neuro-oncology surgery about the diagnosis, treatment, and prevention in an early and accurate way of the Malformation Brainstem Metastasis to avoid the evolution of serious results. In the future, as the aggregate experience of neurosurgeons accrues and as surgical technology improves, the range of patients for whom surgery is a viable option to prevent devastating may expand.

Conflict of Interest

The authors declare no conflicts of interest.

References

1. Sarnat HB, Netsky MG. Evolution of the nervous system. Oxford, UK: Oxford University Press; 1974.
2. Rhoton Jr AL. The posterior fossa cisterns. Neurosurgery. 2000;47(3):S287-97.
3. Basma J, Ryttlefors M, Latini F, Pravdenkova S, Krisht A. Mobilization of the transcavernous oculomotor nerve during basilar aneurysm surgery: biomechanical bases for better outcome. Oper Neurosurg. 2014;10(1):106-15. doi:10.1227/NEU.0000000000000027
4. Bruneau M, Bijlenga P, Reverdin A, Rilliet B, Regli L, Villemure JG, et al. Early surgery for brainstem cavernomas. Acta Neurochir. 2006;148:405-14. doi:10.1007/s00701-005-0671-7
5. Mathiesen T, Edner G, Kihlstrum L. Deep and brainstem cavernomas: a consecutive 8-year series. J Neurosurg. 2003;99(1):31-7. doi:10.3171/jns.2003.99.1.0031
6. Granziera C, Schmahmann JD, Hadjikhani N, Meyer H, Meuli R, Wedeen V, et al. Diffusion spectrum imaging shows the structural basis of functional cerebellar circuits in the human cerebellum *in vivo*. PloS One. 2009;4(4):e5101. doi:10.1371/journal.pone.0005101
7. Johnson JD, Young B. Demographics of brain metastasis. Neurosurg Clin N Am. 1996;7(3):337-44.
8. Matsumoto K, Tada E, Tamesa N, Tomita S, Ohmoto T. Stereotactic brachytherapy for a cystic metastatic brain tumor in the midbrain: Case report. J Neurosurg. 1998;88(1):141-4. doi:10.3171/jns.1998.88.1.0141
9. Adler JR, Cox RS, Kaplan I, Martin DP. Stereotactic radiosurgical treatment of brain metastases. J Neurosurg. 1992; 76(3):444-9. doi:10.3171/jns.1992.76.3.0444
10. Auchter RM, Lamond JP, Alexander III E, Buatti JM, Chappell R, Friedman WA, et al. A multiinstitutional outcome and prognostic factor analysis of radiosurgery for resectable single brain metastasis. Int J Radiat Oncol Biol Phys. 1996;35(1):27-35. doi:10.1016/s0360-3016(96)85008-5
11. Flickinger JC, Kondziolka D, Lunsford LD, Coffey RJ, Goodman ML, Shaw EG, et al. A multi-institutional experience with stereotactic radiosurgery for solitary brain metastasis. Int J Radiat Oncol Biol Phys. 1994;28(4):797-802. doi:10.1016/0360-3016(94)90098-1
12. Flickinger JC, Lunsford LD, Somaza S, Kondziolka D. Radiosurgery: its role in brain metastasis management. Neurosurg Clin N Am. 1996;7(3):497-504. doi:10.1016/s1042-3680(18)30375-9
13. Mehta MP, Rozental JM, Levin AB, Mackie TR, Kubsad SS, Gehring MA, et al. Defining the role of radiosurgery in the management of brain metastases. Int J Radiat Oncol Biol Phys. 1992;24(4):619-25. doi:10.1016/0360-3016(92)90706-n
14. Young RF. Radiosurgery for the treatment of brain metastases. Semin Surg Oncol. 1998;14(1):70-8. doi:10.1002/(SICI)1098-2388(199801/02)14:1<70::AID-SSU9>3.0.CO;2-%23
15. Fuentes S, Delsanti C, Metellus P, Peragut JC, Grisoli F, Regis J. Brainstem metastases: management using gamma knife radiosurgery. Neurosurgery. 2006;58(1):37-42. doi:10.1227/01.NEU.0000190655.95669.5C
16. Yoo TW, Park ES, Kwon DH, Kim CJ. Gamma knife radiosurgery for brainstem metastasis. J Korean Neurosurg Soc. 2011;50(4):299-303. doi:10.3340/jkns.2011.50.4.299
17. Peterson HE, Larson EW, Fairbanks RK, Lamoreaux WT, Mackay AR, Call JA, et al. Gamma Knife radiosurgery treatment for metastatic melanoma of the trigeminal nerve and brainstem: A case report and a review of the literature. Case Rep Neurol Med. 2013;2013:256962. doi:10.1155/2013/256962
18. Fuentes S, Delsanti C, Metellus P, Peragut JC, Grisoli F, Regis J. Brainstem metastases: management using gamma knife radiosurgery. Neurosurgery. 2006;58(1):37-42. doi:10.1227/01.NEU.0000190655.95669.5C
19. Yen CP, Sheehan J, Patterson G, Steiner L. Gamma knife surgery for metastatic brainstem tumors. J Neurosurg. 2006;105(2):213-9. doi:10.3171/jns.2006.105.2.213
20. Lorenzoni JG, Devriendt D, Massager N, Desmedt F, Simon S, Van Houtte P, et al. Brain stem metastases treated with radiosurgery: prognostic factors of survival and life expectancy estimation. Surg Neurol. 2009;71(2):188-95. doi:10.1016/j.surneu.2008.01.029
21. Mei G, Liu X, Song K, Lv Y, Xu M, Xu H, et al. Cyberknife radiosurgery on the brainstem metastases of non-small cell lung cancer. Int J Neurosci. 2021;131(5):462-7. doi:10.1080/00207454.2020.1748622
22. Weil SM, Tew JM. Surgical management of brain stem vascular malformations. Acta Neurochir. 1990;105:14-23. doi:10.1007/BF01664852
23. M. Ziyal, LN Sekhar, E. Salas, C. Sen I. Surgical management of cavernous malformations of the brain stem. Br J Neurosurg. 1999;13(4):366-75. doi:10.1080/02688699943466
24. Zimmerman RS, Spetzler RF, Lee KS, Zabramski JM, Hargraves RW. Cavernous malformations of the brain stem. J Neurosurg. 1991;75(1):32-9. doi:10.3171/jns.1991.75.1.0032
25. Delattre JY, Krol G, Thaler HT, Posner JB. Distribution of brain metastases. Arch Neurol. 1988;45(7):741-4. doi:10.1001/archneur.1988.00520310047016
26. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet. 2004;363(9422):1665-72. doi:10.1016/S0140-6736(04)16250-8
27. Smith ML, Lee JY. Stereotactic radiosurgery in the management of brain metastasis. Neurosurg Focus. 2007;22(3):1-8. doi:10.3171/foc.2007.22.3.6
28. Shaw E, Scott C, Souhami L, Dinapoli R, Kline R, Loeffler J, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. Int J Radiat Oncol Biol Phys. 2000;47(2):291-8. doi:10.1016/S0360-3016(99)00507-6
29. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys. 1997;37(4):745-51. doi:10.1016/s0360-3016(96)00619-0
30. Sperduto PW, Chao ST, Sneed PK, Luo X, Suh J, Roberge D, et al. Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. Int J Radiat Oncol Biol Phys. 2010;77(3):655-61. doi:10.1016/j.ijrobp.2009.08.025
31. Sawaya R, Wildrick DM. Metastatic brain tumors: surgery perspective. Principles and practice of stereotactic radiosurgery. 2008:193-9. doi:10.1007/978-0-387-71070-9_15
32. Yagmurlu K, Rhoton Jr AL, Tanriover N, Bennett JA. Three-dimensional microsurgical anatomy and the safe entry zones of the brainstem. Oper Neurosurg. 2014;10(4):602-20. doi:10.1227/NEU.0000000000000466
33. Cavalheiro S, Yagmurlu K, da Costa MD, Nicacio JM, Rodrigues TP, Chaddad-Neto F, et al. Surgical approaches for brainstem tumors in pediatric patients. Childs Nerv Syst. 2015;31:1815-40. doi:10.1007/s00381-015-2799-y
34. Rangel-Castilla L, Spetzler RF. The 6 thalamic regions: surgical approaches to thalamic cavernous malformations, operative results, and clinical outcomes. J Neurosurg. 2015;123(3):676-85. doi:10.3171/2014.11.JNS14381
35. Cavalcanti DD, Preul MC, Kalani MY, Spetzler RF. Microsurgical anatomy of safe entry zones to the brainstem. J Neurosurg. 2016;124(5):1359-76. doi:10.3171/2015.4.JNS141945
36. Bricolo A. Surgical management of intrinsic brain stem gliomas. Oper Tech Neurosurg. 2000;2(3):137-54. doi:10.10

16/S1092-440X(00)80037-7
37. Cantore G, Missori P, Santoro A. Cavernous angiomas of the brain stem: Intra-axial anatomical pitfalls and surgical strategies. Surg Neurol. 1999;52(1):84-94. doi:10.1016/s0090-3019(99)00036-1
38. Kyoshima K, Kobayashi S, Gibo H, Kuroyanagi T. A study of safe entry zones via the floor of the fourth ventricle for brain-stem lesions: report of three cases. J Neurosurg. 1993;78(6):987-93. doi:10.3171/jns.1993.78.6.0987
39. Bertalanffy H, Benes L, Miyazawa T, Alberti O, Siegel AM, Sure U. Cerebral cavernomas in the adult. Review of the literature and analysis of 72 surgically treated patients. Neurosurg Rev. 2002;25:1-53. doi:10.1007/s101430100179
40. Ozek MM, Tьre U. Surgical approach to thalamic tumors. Childs Nerv Syst. 2002;18:450-6. doi:10.1007/s00381-002-0608-x
41. Yağmurlu K, Zaidi HA, Kalani MY, Rhoton AL, Preul MC, Spetzler RF. Anterior interhemispheric transsplenial approach to pineal region tumors: anatomical study and illustrative case. J Neurosurg. 2017;128(1):182-92. doi:10.3171/2016.9.JNS16279
42. Yağmurlu K, Kalani MY, Rhoton Jr AL. 2 Anatomy of the Brainstem, Thalamus, Pineal Region, and Cranial Nerves. Surgery of the Brainstem. 2019:21.
43. Vogel H. Pathology of the Brainstem, Neurosurgery. 2014;10(Suppl 4):602–619; discussion 619–620.
44. Doorenbosch X, Molloy CJ, David DJ, Santoreneos S, Anderson PJ. Management of cranial deformity following ventricular shunting. Childs Nerv Syst. 2009;25:871-4. doi:10.1007/s00381-009-0842-6
45. Lapras CL, Bognar L, Turjman F, Villanyi E, Mottolese C, Fischer C, et al. Part I: Microsurgery of the tectal plate gliomas. Acta Neurochi. 1994;126:76-83. doi:10.1007/BF01476414
46. Roth J, Chaichana KL, Jallo G, Mirone G, Cinalli G, Constantini S. True aqueductal tumors: a unique entity. Acta neurochir. 2015;157:169-77. doi:10.1007/s00701-014-2264-9
47. Neumann HP, Eggert HR, Weigel K, Friedburg H, Wiestler OD, Schollmeyer P. Hemangioblastomas of the central nervous system: a 10-year study with special reference to von Hippel-Lindau syndrome. J Neurosurg. 1989;70(1):24-30. doi:10.3171/jns.1989.70.1.0024
48. Friedrich C, Warmuth-Metz M, von Bueren AO, Nowak J, Bison B, von Hoff K, et al. Primitive neuroectodermal tumors of the brainstem in children treated according to the HIT trials: clinical findings of a rare disease. J Neurosurg: Pediatr. 2015;15(3):227-35. doi:10.3171/2014.9.PEDS14213
49. Shuto T, Fujino H, Asada H, Inomori S, Nagano H. Gamma knife radiosurgery for metastatic tumours in the brain stem. Acta Neurochir. 2003;145:755-60. doi:10.1007/s00701-003-0034-1
50. Madden J, Foreman NK, Liu AK. Germ cell tumors of the brainstem: report on two cases with pulmonary complications and a review of the literature. J Neuro-oncol. 2009;93:405-8. doi:10.1007/s11060-008-9780-5
51. Araki C. Removal of the pineal tumor. Gekashinryo. 1960;2:517-24.
52. WE D. An operation for the removal of pineal tumors. Surg Gynecol Obstet. 1921;33:113-9.
53. Horrax G. Extirpation of a huge pinealoma from a patient with pubertas praecox: a new operative approach. Arch Neurol Psychiatry. 1937;37(2):385-97. doi:10.1001/archneurpsyc.1937.02260140171009
54. Jamieson KG. Excision of pineal tumors. J Neurosurg. 1971;35(5):550-3. doi:10.3171/jns.1971.35.5.0550
55. Kunicki A. Operative experiences in 8 cases of pineal tumor. J Neurosurg. 1960;17(5):815-23. doi:10.3171/jns.1960.17.5.0815
56. Lazar ML, Clark K. Direct surgical management of masses in the region of the vein of Galen. Surg Neurol. 1974;2(1):17-21.
57. Little KM, Friedman AH, Fukushima T. Surgical approaches to pineal region tumors. J Neuro-oncol. 2001;54:287-99. doi:10.1023/A:1012766902431
58. Poppen JL. The right occipital approach to a pinealoma. J Neurosurg. 1966;25(6):706-10. doi:10.3171/jns.1966.25.6.0706
59. Sekhar LN, Goel A. Combined supratentorial and infratentorial approach to large pineal-region meningioma. Surg Neurol. 1992;37(3):197-201. doi:10.1016/0090-3019(92)90230-K
60. Stein BM. The infratentorial supracerebellar approach to pineal lesions. J Neurosurg. 1971;35(2):197-202. doi:10.3171/jns.1971.35.2.0197
61. Van Wagenen WP. A surgical approach for the removal of certain pineal tumors. Report of a case. Surg Gynecol Obstet. 1931;53:216-20.
62. Sharma MS, Kondziolka D, Khan A, Kano H, Niranjan A, Flickinger JC, et al. Radiation tolerance limits of the brainstem. Neurosurgery. 2008;63(4):728-33. doi:10.1227/01.NEU.0000325726.72815.22
63. Snell JW, Sheehan J, Stroila M, Steiner L. Assessment of imaging studies used with radiosurgery: a volumetric algorithm and an estimation of its error. J Neurosurg. 2006;104(1):157-62. doi:10.3171/jns.2006.104.1.157
64. Bhatnagar AK, Flickinger JC, Kondziolka D, Lunsford LD. Stereotactic radiosurgery for four or more intracranial metastases. Int J Radiat Oncol Biol Phys. 2006;64(3):898-903. doi:10.1016/j.ijrobp.2005.08.035
65. Patchell RA. Metastatic brain tumors. Neurol Clin. 1995;13(4):915-25. doi:10.1016/s0733-8619(18)30025-2
66. Huang CF, Kondziolka D, Flickinger JC, Lunsford LD. Stereotactic radiosurgery for brainstem metastases. J Neurosurg. 1999;91(4):563-8. doi:10.3171/jns.1999.91.4.0563
67. Trifiletti DM, Lee CC, Shah N, Patel NV, Chen SC, Sheehan JP. How does brainstem involvement affect prognosis in patients with limited brain metastases? Results of a matched-cohort analysis. World Neurosurg. 2016;88:563-8. doi:10.1016/j.wneu.2015.10.089
68. Fuentes S, Delsanti C, Metellus P, Peragut JC, Grisoli F, Regis J. Brainstem metastases: management using gamma knife radiosurgery. Neurosurgery. 2006;58(1):37-42. doi:10.1227/01.NEU.0000190655.95669.5C
69. Huang CF, Kondziolka D, Flickinger JC, Lunsford LD. Stereotactic radiosurgery for brainstem metastases. J Neurosurg. 1999;91(4):563-8. doi:10.3171/jns.1999.91.4.0563
70. Hatiboglu MA, Chang EL, Suki D, Sawaya R, Wildrick DM, Weinberg JS. Outcomes and prognostic factors for patients with brainstem metastases undergoing stereotactic radiosurgery. Neurosurgery. 2011;69(4):796-806. doi:10.1227/NEU.0b013e31821d31de
71. Lorenzoni JG, Devriendt D, Massager N, Desmedt F, Simon S, Van Houtte P, et al. Brain stem metastases treated with radiosurgery: prognostic factors of survival and life expectancy estimation. Surg Neurol. 2009;71(2):188-95. doi:10.1016/j.surneu.2008.01.029
72. Hussain A, Brown PD, Stafford SL, Pollock BE. Stereotactic radiosurgery for brainstem metastases: survival, tumor control, and patient outcomes. Int J Radiat Oncol Biol Phys. 2007;67(2):521-4. doi:10.1016/j.ijrobp.2006.08.081
73. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. Jama. 2006;295(21):2483-91. doi:10.1001/jama.295.21.2483
74. Delattre JY, Krol G, Thaler HT, Posner JB. Distribution of brain metastases. Arch Neurol. 1988;45(7):741-4. doi:10.1001/archneur.1988.00520310047016
75. Şenguz M, Kabalay İA, Tezcanlı E, Peker S, Pamir N. Treatment of brainstem metastases with gamma-knife radiosurgery. J Neuro-oncol. 2013;113:33-8. doi:10.1007/s11060-013-1086-6
76. Emami B, Lyman J, Brown A, Cola L, Goitein M, Munzenrider JE, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys. 1991;21(1):109-22. doi:10.1016/0360-3016(91)90171-Y
77. Koyfman SA, Tendulkar RD, Chao ST, Vogelbaum MA, Barnett GH, Angelov L, et al. Stereotactic radiosurgery for single brainstem metastases: the cleveland clinic experience. Int J Radiat Oncol Biol Phys. 2010;78(2):409-14. doi:10.1016/j.ijrobp.2009.07.1750
78. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys. 1997;37(4):745-51. doi:10.1016/s0360-3016(96)00619-0
79. Kawabe T, Yamamoto M, Sato Y, Barfod BE, Urakawa Y, Kasuya H, et al. Gamma Knife surgery for patients with brainstem metastases. J Neurosurg. 2012;117(Special_Suppl):23-30. doi:10.3171/2012.7.GKS12977
80. Kilburn JM, Ellis TL, Lovato JF, Urbanic JJ, Daniel Bourland J,

Munley MT, et al. Local control and toxicity outcomes in brainstem metastases treated with single fraction radiosurgery: is there a volume threshold for toxicity?. J Neuro-oncol. 2014;117:167-74. doi:10.1007/s11060-014-1373-x

81. Lorenzoni JG, Devriendt D, Massager N, Desmedt F, Simon S, Van Houtte P, et al. Brain stem metastases treated with radiosurgery: prognostic factors of survival and life expectancy estimation. Surg Neurol. 2009;71(2):188-95. doi:10.1016/j.surneu.2008.01.029

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