# Optimal management of brainstem metastases: a narrative review

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**Background and Objective:** Brainstem metastases comprise fewer than 7% of all brain metastases. Nonetheless, they present clinicians with unique clinical challenges in symptom management and treatment. No comprehensive review summarizing the management of brainstem metastases exists. This review aims to summarize epidemiology, anatomy, clinical correlation, prognosis, options for management of symptoms, treatment, treatment toxicity, and dose and fractionation for brainstem stereotactic radiosurgery (SRS) as reported in the literature.

**Methods:** In July 2021, we searched PubMed and Embase for retrospective studies of brainstem metastasis treatment, as well as case series and case reports describing diagnosis and clinical management of brainstem metastasis. Keywords and MeSH terms searched included "brainstem metastasis", "symptomatic brainstem metastasis", "brain metastasis", "stereotactic radiosurgery brainstem", "whole brain radiation brainstem", "brainstem metastasis resection", "brainstem radiation toxicity", "brainstem radiosurgery toxicity", "brainstem radiosurgery dose", and "radiosurgery dose tolerance". Titles and abstracts were screened for relevant articles and studies. References from full-text articles were screened for additional studies.

**Key Content and Findings:** Single-institution studies and multicenter retrospective analyses from 1993 to 2021 reflect a shift from reliance on whole-brain radiation therapy (WBRT) to SRS for primary treatment of brainstem metastases. Recent multicenter retrospective analyses and single-institution case series support the safety and efficacy of SRS of brainstem metastases in symptom management and preservation of quality of life. Incidence of radiation-induced toxicity following SRS of brainstem metastases is comparable to that of SRS for other brain metastases. Complications following brainstem SRS are most strongly associated with prior WBRT.

**Conclusions:** Radiation oncologists play a central role in the treatment of brainstem metastases due to reliance on SRS. Dose and fractionation of brainstem SRS remain largely institution-dependent. The field would benefit from inclusion of brainstem metastases in prospective trials of SRS and studies of adverse effects of salvage WBRT after prior SRS of brainstem metastases.

**Keywords:** Brainstem metastasis; stereotactic radiosurgery (SRS); brainstem dose tolerance; brainstem radiation toxicity

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## Introduction

Brain metastases represent the most common neurologic complication of cancer patients with fewer than 7% of all brain metastases found in the brainstem. Historically, brainstem metastases were treated with whole-brain radiation therapy (WBRT) alone, as the density of nuclei and white matter tracts in the region rendered surgical resection and early targeted radiation prohibitively high risk for serious adverse effects. Prospective clinical trials of stereotactic radiosurgery (SRS) for brain metastases also excluded brainstem metastases due to caution with SRS radiation doses and the perceived radiosensitivity of brainstem. Nonetheless, single-institution case series of brainstem metastasis SRS emerged with encouraging findings of safety and efficacy. Recent analyses of multicenter retrospective data support the safety and efficacy of SRS for brainstem metastases and shed light on trends in adverse events after brainstem SRS. This review will outline the pathophysiology of brainstem metastases and their clinical manifestations, historical treatment paradigms, and contemporary trends in management. We present the following article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-21-146/rc).

## Methods

PubMed and Embase were used to compile retrospective studies of brainstem metastasis treatment, case series and case reports describing diagnosis of brainstem management, and case series and case reports describing clinical management of brainstem metastasis on July 1, 2021 (*Table 1*). Keywords and MeSH terms searched included "brainstem metastasis", "symptomatic brainstem metastasis", "brain metastasis", "stereotactic radiosurgery brainstem", "whole brain radiation brainstem", "brainstem metastasis resection", "brainstem radiation toxicity", "brainstem radiosurgery toxicity", "brainstem radiosurgery dose", and "radiosurgery dose tolerance". Titles and abstracts were screened for relevant articles and studies. References from full-text articles were screened for additional studies. Case reports and case series describing symptomatic brainstem metastasis were included only if the symptomatic neurologic deficit was attributed to a brainstem metastasis. Retrospective cohort studies that were conducted before 2007 were excluded. All co-authors contributed, reviewed, and approved the selected literature for this review.

## Epidemiology

The literature has reported that 80–85% of brain metastases are located in the cerebral hemisphere, 10–15% in the cerebellum and 3–7% in the brainstem (1-4). The lower incidence of brainstem metastases relative to other brain metastases is attributed to the small volume of the brainstem (less than 3% of the brain by weight) and greater distribution of arterial perfusion to the anterior circulation, which supplies the cerebral hemispheres, over the posterior circulation that supplies the brainstem and cerebellum. High resolution phase contrast magnetic resonance imaging (MRI) studies revealed that 72% of intracranial arterial

**Table 1** Methods for selection of literature included in this review

| Items | Specification |
|---|---|
| Date of search | July 1, 2022 |
| Databases and other sources searched | PubMed, Embase |
| Search terms used | Brainstem metastasis, symptomatic brainstem metastasis, brain metastasis, stereotactic radiosurgery brainstem, whole brain radiation brainstem, brainstem metastasis resection, brainstem radiation toxicity, brainstem radiosurgery toxicity, brainstem radiosurgery dose, radiosurgery dose tolerance |
| Timeframe | For case reports and case series: 1950–2014. For retrospective cohort studies: 2007–2021 |
| Inclusion and exclusion criteria | All retrospective cohort studies were English language. All case reports on symptomatic brainstem metastasis must have explicitly attributed a neurological deficit to the brainstem metastasis |
| Selection process | All authors contributed and reviewed the selected literature |
| Any additional considerations, if applicable | None |

perfusion is received through the internal carotid arteries (anterior circulation), while 28% is received through the vertebral arteries (posterior circulation) (5).

The pons is the most common location of brainstem metastasis, followed by the midbrain, and then the medulla (6,7). The largest existing analysis of multicenter retrospective data reports that the most frequently associated primary malignancies are lung (44.9%, predominantly non-small cell), followed by breast (20.2%), melanoma (10%), renal cell/genitourinary (7.5%), and gastrointestinal (GI) cancers (4.5%). These incidences are similar to those found in a classical autopsy study of brainstem metastases (46.7% lung, 13.3% breast, 8.9% melanoma, 4.5% renal cell, 4.5% GI), as well as the incidences of primary malignancies for all brain metastases (50% lung cancer, predominantly non-small cell, 15% breast, 7% melanoma, 7% renal cell, and 6% GI) (2,4).

## Brainstem anatomy

Superiorly to inferiorly, the brainstem is composed of the diencephalon, midbrain, pons, and medulla oblongata. These structures are densely populated by nuclei and white matter tracts that allow communication among the cerebral hemispheres, cerebellum, and spinal cord. The major white matter tracts that travel through the brainstem are the reticular formation, pontocerebellar tract, corticospinal and corticobulbar motor tracts, spinothalamic tract, dorsal column/medial lemniscus, lateral lemniscus, trigeminal lemniscus, and spinotrigeminal tract.

The diencephalon flanks the third ventricle and contains the epithalamus, subthalamus, hypothalamus, and thalamus. Notable structures include the pineal gland, mammillary bodies, nucleus of Meynert, subthalamic nucleus, lateral geniculate nucleus, and medial geniculate nucleus. The diencephalon is involved in memory consolidation, sensory integration, modulation of motor activity, and regulation of consciousness.

The midbrain envelops the cerebral aqueduct connecting the third and fourth ventricles. Notable structures include the superior and inferior colliculi, medial longitudinal fasciculus, substantia nigra, red nucleus, dorsal raphe nucleus, periaqueductal grey, and the nuclei of cranial nerves (CNs) III and IV. The midbrain is involved in visual and auditory processing, oculomotor reflexes, coordination of eye movements, and motor regulation (substantia nigra, red nucleus).

The pons connects the midbrain with the medulla and cerebellum. Notable structures include the locus coeruleus, pontine nucleus, and the nuclei of CNs V, VI, VII, and VIII. The pontine structures are involved in coordination, autonomic functions, hearing, taste, facial sensation and motor function.

The medulla connects the pons to spinal cord and abuts the fourth ventricle. The nucleus solitarius, cardiovascular, respiratory, vomiting, and vasomotor centers contribute to the autonomic nervous system. The nucleus ambiguus and inferior salivary nucleus regulate swallowing. The gracile and cuneate nuclei, also known as the dorsal column nuclei, integrate sensory input from the dorsal column-medial lemniscus pathway. The medullary pyramids carry motor fibers of the corticobulbar and corticospinal tracts. The olivary bodies and vestibular nucleus regulate coordination and equilibrium. The nuclei of CNs IX, X, XI, and XII are located in the medulla.

## Clinical presentation

Nearly half of brainstem metastases are asymptomatic upon discovery, in part due to the sensitivity of MRI and its frequent use in workup and follow-up imaging of patients with cancer. Symptomatic brainstem metastases result from direct impingement of nuclei, tracts, or CNs caused by mass effect or vasogenic edema. In a pooled meta-analysis of 22 single-institution studies, Chen and colleagues reported that 49% of brainstem metastases among 1,104 patients were symptomatic at diagnosis, with a 46.8% median incidence of symptomatic brainstem metastasis among the studies (7). Reports of brainstem-localizing signs in the literature are summarized in *Table 2* (8-14). Specifically, involvement of the corticospinal tract can result in hemiparesis while hemisensory loss can result from damage to the medial lemniscus. Ataxia can result from disruption of brainstem-cerebellum communication. CN palsies can be caused by lesions of the CN nuclei, internuclear connections or efferent fibers. *Figure 1* demonstrates post-gadolinium MRI imaging of a symptomatic metastatic lesion to the pons.

## Prognosis

The median survival time of patients with brainstem metastases left untreated has been reported as 1 month (15,16). The prognosis improves for patients who receive treatment but depends on the intracranial response to treatment as well as control of extracranial disease. On multi-institutional analysis of patients treated with radiosurgery for brainstem metastases, median survival

**Table 2** Symptomatic brainstem metastases reported in the literature

| Author | Presenting symptom(s) | No. of patients | Location of metastasis | Intervention | Primary tumor |
|---|---|---|---|---|---|
| Awad | Headache, tinnitus, ataxia, RUE paresthesia, bilateral dysmetria, hyperreflexia, gait disturbance | 1 | Pontomedullary | Resection and trastuzumab | Breast carcinoma |
| Straube | Dysarthria, psychic aura, nystagmus | 1 | Pontomedullary | None | Lung carcinoma |
| Derby | Headache, light-headedness, bilateral lower extremity weakness, dysarthria, tremor, horizontal conjugate gaze palsy nausea, vomiting | 1 | Intra-axial | None | Renal clear cell |
| Karampelas | Hemiballismus | 1 | Subthalamic nucleus | GKRS 18 Gy to 50% isodose line, topiramate 50 mg BID | Breast carcinoma |
| Glass | Hemiballismus | 1 | Subthalamic nucleus | None | Lung adenocarcinoma |
| Moore | Hemiballismus | 1 | Left frontal, right occipital, pontine, cerebellar, and bilateral thalamic | – | Lung |
| Vale | Hemiballismus | 1 | Left subthalamus | WBRT, risperidone | Breast carcinoma |
| Hunter | Hemiparesis | 11 | Unknown | Unknown | Unknown |
| Hunter | CN III palsy | 3 | Unknown | Unknown | Unknown |
| Hunter | CN IV palsy | 2 | Unknown | Unknown | Unknown |
| Hunter | CN V palsy | 3 | Unknown | Unknown | Unknown |
| Tomecek | CN VI palsy, nystagmus, ataxia, obstructive hydrocephalus | 1 | Dorsal rostral aspect of the midbrain | Dexamethasone, VP shunt, resection, phenytoin | Kidney adenocarcinoma |
| Hunter | CN VI palsy | 4 | Unknown | Unknown | Unknown |
| Reyes | CN VI palsy (binocular horizontal diplopia) | 1 | Right pons | Radiation | Breast carcinoma |
| Derby | CN VII palsy, L sided headache, nausea, vomiting, hemibody weakness, sensory impairment | 1 | Mesencephalopontine, pontomedullary | None | Undifferentiated lung |
| Hunter | CN VII palsy | 4 | Unknown | Unknown | Unknown |
| Hunter | Dysconjugate gaze | 3 | Unknown | Unknown | Unknown |
| Inci | Locked-in syndrome | 1 | Pontomedullary | Resection | Melanoma |
| Pogacar | Locked-in syndrome | 1 | Pontomedullary | None | Lung adenocarcinoma |
| Hunter | Ataxia | 5 | Unknown | Unknown | Unknown |
| Derby | Ataxia, R sided falling, RUE numbness, gaze deviation, unilateral hearing loss | 1 | Tegmentum | None | Lung adenocarcinoma |
| Hunter | Hemisensory loss | 2 | Unknown | Unknown | Unknown |
| Hunter | Obstructive hydrocephalus | 4 | Unknown | Unknown | Unknown |

RUE, right upper extremity; CN, cranial nerve; L sided, left sided; R sided, right sided; GKRS, gamma Knife radiosurgery; BID, twice daily; WBRT, whole brain radiation therapy; VP, ventriculo-peritoneal.

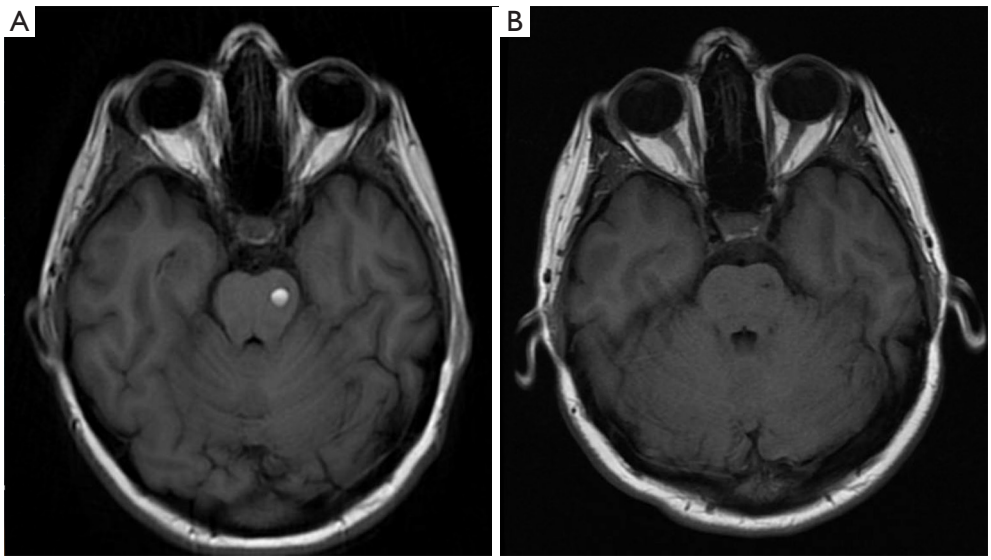


**Figure 1** Axial T1-weighted MRI of pontine metastasis before and after radiosurgery. (A) Melanoma metastatic to the pons resulting in a 6 mm left pontine lesion causing hemiparesis. (B) This lesion was treated with single fraction linear accelerator-based radiosurgery, and 6 months later, the lesion involuted and resolved. MRI, magnetic resonance imaging.

was 5.6 months, and 1-year survival was 32.7%. Chen and colleagues report an objective response rate of 59% in 642 patients across 17 studies (7). The 1-year local control rate was 86% in 1,410 patients across 31 studies who had brainstem metastases treated with SRS. There was a 33% 1-year overall survival in 1,254 patients across 27 studies and 2-year survival of 13% in 959 patients across 22 studies. Only 2.7% of deaths after treatment were attributable to progression of the brainstem metastasis, among 703 patients pooled from 19 studies; 68.6% died from systemic disease, and 18.7% died from non-brainstem intracranial disease (7).

Various studies have associated longer survival with control of extracranial disease, higher Karnofsky performance status (KPS), and class I or II recursive partitioning analysis (RPA) at time of treatment (16-23). Other favorable prognostic factors have been reported without consensus in the literature, including lower number of brain metastases, non-melanoma histology and smaller tumor volume (8,24,25).

## Symptom management

Currently, SRS is the definitive mode of alleviating symptomatic brainstem metastasis.

Chen and colleagues reported a 55% symptom improvement rate in 323 patients across 13 studies (7). Some clinical manifestations of brainstem metastasis may require management in the interim before radiosurgery. Corticosteroids and anti-epileptic drugs (AEDs) are the mainstays of symptomatic management of brain metastasis, though some patients may require a shunt. The Congress of Neurological Surgeons Evidence-Based Guidelines recommend starting 4 to 8 mg/d of dexamethasone for mild symptoms of elevated intracranial pressure and peritumoral edema secondary to brain metastases and higher doses such as 16 mg/d for severe symptoms (26). In patients with impaired consciousness or other severe signs of elevated intracranial pressure, Sawaya and colleagues report that headache and neurologic deficits may respond to corticosteroids within 1 day and full effect within 48 hours (27). Steroid doses should be tapered as soon as possible as tolerated to minimize adverse effects of long-term corticosteroid use. The benefits and harms of corticosteroid use must be carefully considered if used concurrently with immune checkpoint inhibitors. Baseline corticosteroid use of ≥10 mg of prednisone equivalent has been associated with inferior outcomes in patients with non-small-cell lung cancer (NSCLC) treated with PD-(L)1 blockade (28,29).

Brainstem seizures are generally rare, brief episodes (15–60 seconds) of sensory and motor disturbance with a tonic-algetic and akinetic-atonic pattern without loss of consciousness. Electroencephalogram (EEG) typically

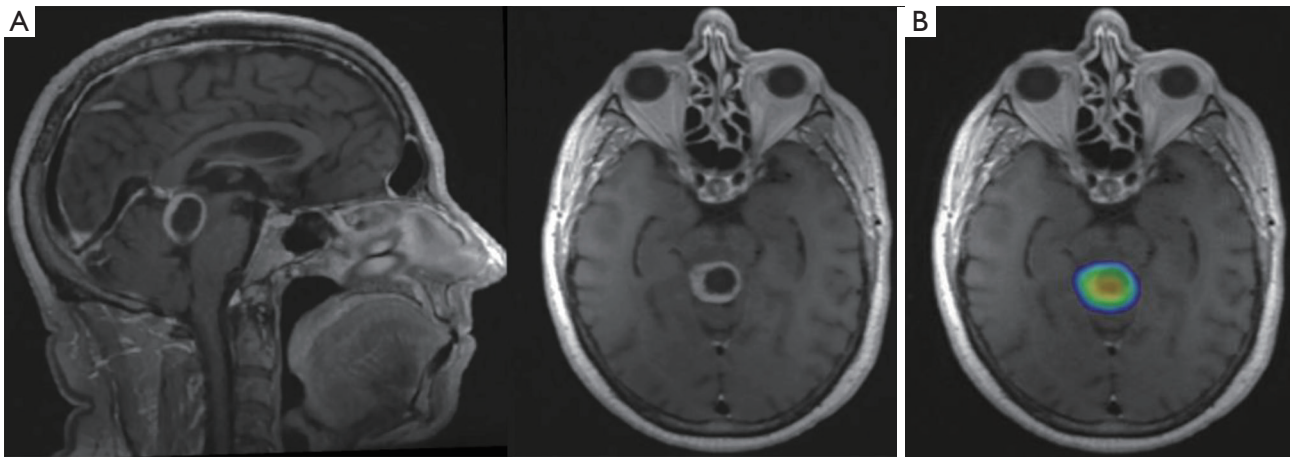


**Figure 2** T1-weighted MRI images of metastasis in close proximity to midbrain and pons. (A) Sagittal and axial images of patient with melanoma metastatic to the cerebral aqueduct posterior to the midbrain and pons. (B) This lesion was treated with 27 Gy in 3 fractions of linear accelerator-based radiosurgery. MRI, magnetic resonance imaging.

demonstrates a normal pattern with occasional, transient decreases of amplitude. Carbamazepine, valproic acid, and phenytoin are effective AEDs for brainstem seizures (30).

## Treatment

Surgical resection of brainstem metastases is seldom attempted due to high risks of operating on the brainstem, as it is critical for neurologic function and injury can result in severe neurologic symptoms or death (31-33). Brainstem metastases have largely been excluded from prospective trials of SRS for treatment of brain metastases due to concern that brainstem toxicity would result from radiation doses that are acceptable in the remainder of the brain (34,35).

Whole-brain and targeted radiation therapy techniques were initially utilized as the primary treatment options for brainstem metastases. A single-institution study of SRS for metastatic melanoma in 1993 described four cases of brainstem SRS (36). Subsequent case series presented evidence of efficacy and safety of SRS for brainstem metastases (37-39). Single-institution retrospective studies have provided useful information on local control, median survival, and adverse events (8,9,18,24,40-47). Koyfman and colleagues at Cleveland Clinic described a series of 43 patients with single brainstem metastases who underwent SRS as the first local treatment (21 patients) or as salvage after previous WBRT (22 patients) (47). These patients were treated at a median prescription dose of 15 (range, 9.6–24) Gy with a mean conformality index of 1.7 and mean heterogeneity index of 1.9. Of the 33 patients with post-treatment MRI scans, radiographic radionecrosis was demonstrated in 2 (6%) patients. No grade 3 or 4 toxicities were observed. Grade 1 or 2 weakness, ataxia, and bleeding from a pin site were noted in 3 patients.

At the time of this review, two multi-institutional analyses of brainstem metastases treated with SRS have been conducted. Trifiletti and colleagues (47) obtained and analyzed the data of 547 patients with 596 SRS-treated brainstem metastases from collaborators in the International Gamma Knife Research Foundation. This cohort had a median dose of 16 Gy prescribed to the 50% isodose line and a median maximum dose of 30 Gy. At 1 year after SRS, local control was achieved in 81.8% of tumors and overall survival at 1 year after SRS was 32.7%. 7.4% of patients experienced treatment-related grade 3 or higher toxicities (47). Most recently, Chen and colleagues (7) conducted a meta-analysis of data from 32 retrospective studies that included 1,446 patients with 1,590 brainstem metastases, not including the patients described in the 2016 multicenter retrospective study by Trifiletti and colleagues (47). The brainstem metastases were treated with a median marginal dose of 16 (range, 11–39) Gy in a median of 1 (range, 1–13) fraction. Local control was achieved in 86% of lesions at 1 year in 1,410 patients across 31 studies, and the 1-year overall survival rate was 33% in 1,254 patients across 27 studies. Grade 3 to 5 treatment related toxicities were noted in 2.4% of 1,421 patients across 31 studies. The objective response rate was 59% in 642 patients across 17 studies and 55% of patients had improvement in their symptoms in 323 patients across 13 studies (7). *Figures 2,3* illustrate treatment plans of solitary brainstem metastases.

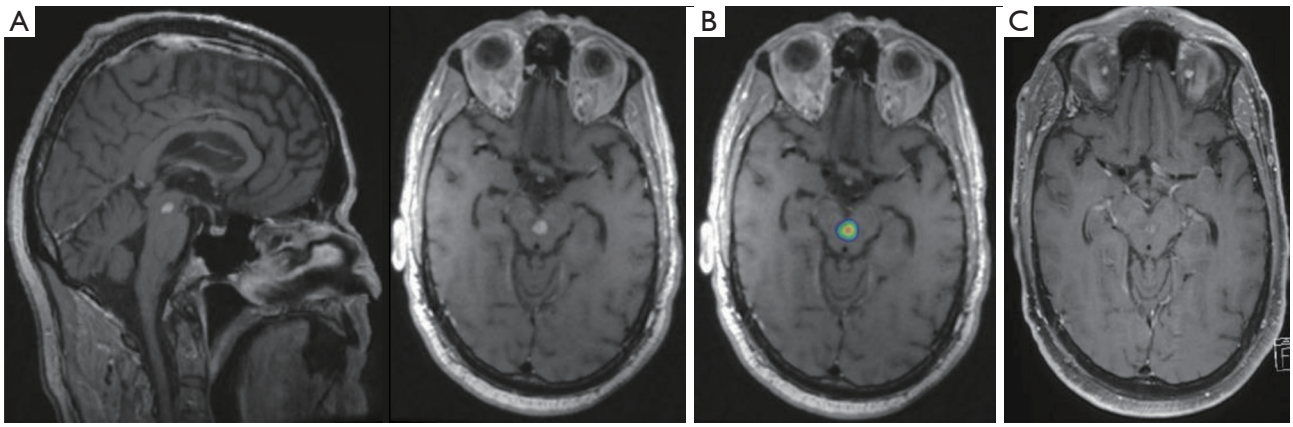


**Figure 3** T1-weighted MRI images of patient with a metastatic lesion in midbrain, before and after radiosurgery. (A) Sagittal and axial images of patient with lung adenocarcinoma metastatic to the central midbrain, (B) treated with 27 Gy in 3 fractions of linear accelerator-based radiosurgery. (C) Significant decrease in size and gadolinium enhancement was noted 6 months following radiosurgery. MRI, magnetic resonance imaging.

## Dosage

SRS is often delivered in a single fraction, but may also be given in 2 to 5 fractions for larger targets or those near critical normal tissues such as the brainstem. No guidelines exist for tumor margin dose selection of SRS for brainstem metastases which is currently institution-dependent. Conflicting findings exist regarding the optimum margin dose, with some reports of correlation between higher marginal dose and longer survival (16,42), although this may be at the expense of greater toxicity. Valery and colleagues reported a local control rate of 90% and median survival time of 10 months with a median marginal dose of only 13.4 Gy. Other series have recommended tumor margin doses as low as 12 Gy (48). Factors influencing dose selection include tumor volume, tumor histology, and prior radiotherapy (44,49). Additionally, the radiosurgical technology used (Gamma Knife versus linear accelerator-based radiosurgery) impacts the rate of dose fall-off which influences the margin dose.

Regarding doses for single fraction SRS for brainstem metastases, experts have recommended margin doses of 20 Gy for lesions <1 cc, 18 Gy for 1–2 cc lesions, and 15 Gy for lesions >2 cc. Other regimens in the literature for the tumors in or near the brainstem include 27 Gy in 3 fractions and 25–31 Gy in 5 fractions (50). The brainstem maximum point set by Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC), which was based solely on single-fraction SRS data, indicates that 12.5 Gy in one fraction carries a <5% risk of brainstem injury, though other studies have indicated that a maximum brainstem dose of 15–20 Gy carries a low risk of injury (35). The American Association of Physicists in Medicine (AAPM) Task Group 101 report recommends a maximum brainstem dose of <23.1 Gy in 3 fractions and ≤31 Gy in 5 fractions (51). The AAPM Working Group on Biological Effects of Hypofractionated Radiotherapy/stereotactic body radiation therapy (SBRT) HyTEC study [2021] explicitly omitted studies that focused on brainstem toxicity and did not report specific recommendations or dose-volume metrics predictive of brainstem toxicity (52).

## Safety/toxicity

Edema, hemorrhage, and radionecrosis are the underlying mechanisms of adverse events following SRS. The most frequently reported toxicities after brainstem SRS are postprocedure headache (which may be associated with head frame placement), fatigue, nausea, vomiting, which are usually self-limited or effectively treated with corticosteroids (40,48). Confusion, ataxia, weakness, focal neurologic deficits, and seizures have also been reported (24,41,42,45). Yoo and colleagues reported one death from a hemorrhagic tumor following Gamma Knife SRS to a pontine lesion treated with 14.8 Gy (22). Adverse effects that were reported in the literature are summarized in *Table 3*. A case of radiation necrosis after WBRT with SRS boost to brainstem metastasis is described in *Figure 4*. Despite steroids, there was progression of the presumed radiation necrosis. She

**Table 3** Acute toxicities following brainstem SRS

| Author | Presenting symptom | Radiologic finding | Treatment | Toxicity grade | Tumor histology | Prior WBRT | Dose (Gy) | Toxicity frequency | Total patients in study |
|---|---|---|---|---|---|---|---|---|---|
| Kelly | Altered mental status | Unknown | Steroids | Grade 3 | Unknown | Unknown | Unknown | 1 | 24 |
| Kilburn | Ataxia | Radiation necrosis | Steroids | Grade 1–2 | NSCLC | No | 18 | 2 | 44 |
| Kelly | Ataxia | Unknown | Steroids | Grade 3 | Unknown | Unknown | Unknown | 1 | 24 |
| Koyfman | Ataxia | Unknown | Unknown | Grade 1–2 | Unknown | Unknown | Unknown | 1 | 43 |
| Kilburn | Ataxia and diplopia | Radiation necrosis | Bevacizumab | Grade 3 | Adenocarcinoma, unknown primary | No | 18 | 1 | 44 |
| Kawabe | Ataxia, death | Edema | Unknown | Grade 5 | NSCLC | No | 18 | 1 | 200 |
| Kased | Ataxia, dysequilibrium, and left facial numbness | Radiation necrosis | Unknown | Grade 3 | RCC | No | 12 | 1 | 42 |
| Hatiboglu | CN palsy | Unknown | Unknown | Grade 1–2 | Unknown | Unknown | Unknown | 2 | 60 |
| Lin | CN V palsy | Radiation necrosis | Unknown | Grade 3 | Unknown | Unknown | 17 | 1 | 45 |
| Nakamura | CN VI palsy | Edema | Unknown | Grade 1–2 | Unknown | Unknown | Unknown | 1 | 20 |
| Lin | CN VII palsy | Unknown | Unknown | Grade 3 | Unknown | Unknown | 12 | 1 | 45 |
| Winograd | CN VII palsy | Unknown | Steroids, bevacizumab | Grade 3 | Endometrial | Unknown | Unknown | 1 | 41 |
| Kilburn | Diplopia | Unknown | Steroids | Grade 3 | Ovarian | No | 18 | 1 | 44 |
| Kilburn | Diplopia and dysphagia | Unknown | Steroids | Grade 3 | NSCLC | No | 17 | 1 | 44 |
| Voong | Gait disturbance | Edema | Steroids | Grade 3 | Sarcoma | Unknown | 18 | 1 | 74 |
| Voong | Gait disturbance | Edema | Unknown | Grade 3 | Melanoma | Unknown | 15 | 1 | 74 |
| Voong | Headache | Edema | Unknown | Grade 1–2 | Melanoma | Unknown | 14 | 1 | 74 |
| Leeman | Headache | Unknown | Steroids | Grade 1–2 | Unknown | Unknown | Unknown | 2 | 36 |
| Valery | Headache | Unknown | Steroids | Grade 1–2 | Unknown | Unknown | Unknown | 4 | 30 |
| Hatiboglu | Headache | Unknown | Unknown | Grade 1–2 | Unknown | Unknown | Unknown | 3 | 60 |
| Voong | Headache, vomiting | Hemorrhage and radiation necrosis | Pentoxifylline | Grade 3 | Lung | Unknown | 16 | 1 | 74 |
| Joshi | Hemiparesis | Unknown | Unknown | Grade 3 | NSCLC | Unknown | 14 | 1 | 48 |
| Joshi | Hemiparesis | Unknown | Steroids | Grade 3 | SCLC | Unknown | 15 | 1 | 48 |
| Hussain | Hemiparesis | Unknown | Unknown | Grade 3 | Unknown | Yes | 18 | 1 | 22 |

**Table 3** (*continued*)

**Table 3** (*continued*)

| Author | Presenting symptom | Radiologic finding | Treatment | Toxicity grade | Tumor histology | Prior WBRT | Dose (Gy) | Toxicity frequency | Total patients in study |
|---|---|---|---|---|---|---|---|---|---|
| Winograd | Hemiparesis | Edema | Steroids, bevacizumab | Grade 3 | Unknown | Unknown | 16 | 1 | 41 |
| Kased | Hemiparesis | Hemorrhage | Unknown | Grade 3 | RCC | Yes | 16 | 1 | 42 |
| Hatiboglu | Hemiparesis | Unknown | Unknown | Grade 1–2 | Unknown | Unknown | Unknown | 2 | 60 |
| Hatiboglu | Hemiparesis | Unknown | Unknown | Grade 3 | Unknown | Unknown | Unknown | 1 | 60 |
| Kased | Hemiparesis | Unknown | Unknown | Grade 3 | Unknown | Yes | 15 | 1 | 42 |
| Hatiboglu | Hemiparesis, CN palsy | Hemorrhage | Unknown | Grade 3 | Unknown | Unknown | Unknown | 1 | 60 |
| Trifiletti | Hemiplegia, loss of consciousness | Radiation necrosis, edema | Unknown | Grade 3 | RCC | No | 18 | 1 | 161 |
| Voong | Horner' syndrome, visual disturbance | Radiation necrosis | Bevacizumab | Grade 3 | Breast | Unknown | 16 | 1 | 74 |
| Nakamura | ICH | Hemorrhage | Steroids | Grade 3 | Melanoma | Unknown | Unknown | 1 | 20 |
| Trifiletti | ICH and death | Hemorrhage | Steroids | Grade 5 | Melanoma | No | 20 | 1 | 161 |
| Peterson | ICH and death | Hemorrhage | Steroids | Grade 5 | Melanoma | Unknown | Unknown | 1 | 1 |
| Yoo | ICH and death | Hemorrhage | Steroids | Grade 5 | Melanoma | No | 14.8 | 1 | 32 |
| Murray | Leg pain, dizziness, speech difficulty | Radiation necrosis | Steroids, hyperbaric oxygen | Grade 3 | Unknown | Yes | 15 | 1 | 44 |
| Voong | Leg weakness and imbalance | Edema | Unknown | Grade 3 | Thyroid | Unknown | 20 | 1 | 74 |
| Sugimoto | Nausea | Unknown | Steroids | Grade 1–2 | Unknown | Unknown | Unknown | 1 | 24 |
| Leeman | Nausea | Unknown | Steroids | Grade 1–2 | Unknown | Unknown | Unknown | 1 | 74 |
| Huang | Nausea, vomiting, dizziness | Unknown | Unknown | Grade 1–2 | Unknown | Unknown | Unknown | 4 | 26 |
| Hatiboglu | Nausea, vomiting | Unknown | Unknown | Grade 1–2 | Unknown | Unknown | Unknown | 1 | 60 |
| Hatiboglu | Nausea, vomiting | Unknown | Unknown | Grade 1–2 | Unknown | Unknown | Unknown | 1 | 60 |
| Hatiboglu | Nausea, vomiting | Unknown | Unknown | Grade 1–2 | Unknown | Unknown | Unknown | 1 | 60 |
| Guney | Pyramidal motor syndrome | Unknown | Unknown | Grade 3 | Unknown | Unknown | Unknown | 1 | 21 |
| Nakamura | Pyramidal motor syndrome | Edema | Unknown | Grade 1–2 | Unknown | Unknown | Unknown | 2 | 20 |

**Table 3** (*continued*)

**Table 3** (*continued*)

| Author | Presenting symptom | Radiologic finding | Treatment | Toxicity grade | Tumor histology | Prior WBRT | Dose (Gy) | Toxicity frequency | Total patients in study |
|---|---|---|---|---|---|---|---|---|---|
| Murray | Quadriparesis | Radiation necrosis | Steroids | Grade 3 | Unknown | Yes | 15 | 1 | 44 |
| Huang | Seizure | Unknown | AED | Grade 3 | Unknown | Unknown | Unknown | 3 | 26 |
| Koyfman | Weakness | Unknown | Unknown | Grade 1–2 | Unknown | Unknown | Unknown | 1 | 43 |

SRS, stereotactic radiosurgery; CN, cranial nerve; ICH, intracranial hemorrhage; AED, anti-epileptic drug; NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma; SCLC, small-cell lung cancer; WBRT, whole-brain radiation therapy.

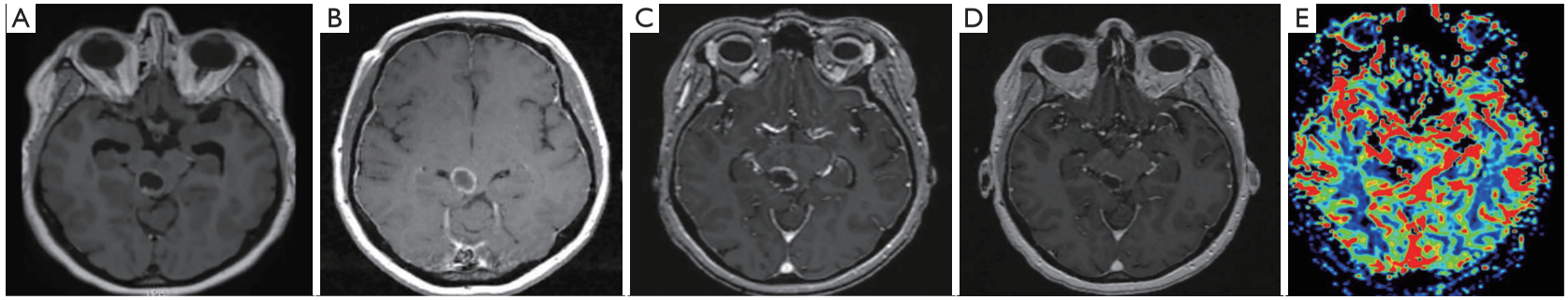


**Figure 4** A 52-year-old female with 1.2 cm diameter midbrain metastasis from squamous cell lung cancer, treated with WBRT to 37.5 Gy with SRS boost of 15 Gy to the brainstem metastasis. (A) MRI at diagnosis of brain metastasis. (B) MRI at time of SRS boost. (C) MRI 4 months post-SRS shows improvement. (D) MRI and (E) MR perfusion images consistent with radiation necrosis after patient developed worsening headaches (note negative cerebral blood volume). WBRT, whole-brain radiation therapy; SRS, stereotactic radiosurgery; MRI, magnetic resonance imaging; MR, magnetic resonance.

subsequently passed away with an abrupt decline in her functional and neurologic status.

Rates of adverse events after brainstem SRS ranged from 0% to 27% in 31 single-institution retrospective studies analyzed by Chen and colleagues, with an overall 5.6% rate of symptomatic adverse effects and 2.4% rate of grade 3 to 5 toxicities in 1,421 patients (7).

Trifiletti and colleagues (47) reported that 7.4% of their cohort experienced grade 3–5 toxicities. These rates are comparable to the 3–8% toxicity rates reported in prospective randomized/observational trials for SRS for all brain metastases. However, brainstem SRS appears to have a shorter median time to development of toxicity (3 months) compared to cerebral lesions (4.5 months) (53).

Individual risk factors, particularly prior WBRT, may influence the incidence of posttreatment toxicities. Of the 44 patients in the Trifiletti study (47) who developed a severe toxicity, 84% had undergone WBRT before brainstem SRS. The authors also found that an interval of at least 4.5 months between WBRT and brainstem SRS was associated with lower risk of toxicity (odds ratio, 0.116). Increased tumor volume and higher margin dose have also been reported as risk factors (18).

## Conclusions

Brainstem metastases pose challenging clinical problems in the setting of various primary malignancies. The radiation oncologist occupies a central role in the treatment of brainstem metastases, perhaps even more than in the treatment of metastatic disease in other regions of the brain, due to the inoperability of the brainstem. Despite the exclusion of brainstem metastases from prospective trials of SRS, single-institution reports on brainstem SRS consistently demonstrated improvement or prevention of symptoms secondary to brainstem lesions, preservation of quality of life, and toxicity rates that are comparable to those of SRS for other brain metastases. A compelling rationale therefore exists for inclusion of brainstem metastases in future prospective trials of SRS to develop optimal dose and fractionation schemes. Dose and fractionation for brainstem SRS remain institution-dependent with some guidelines. The extant literature demonstrates that complications following brainstem SRS are most strongly associated with prior WBRT. As WBRT is used less frequently as the initial mode of treatment for brain metastases, toxicity following brainstem SRS may be of lesser concern. However, future studies may examine adverse effects of WBRT for salvage therapy after prior SRS of brainstem metastases.

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