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Stereotactic Radiosurgery is a Safe and Effective Method of Prolonging Survival and Managing Symptoms in Patients with Brainstem Metastases

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Abstract

Metastases are the most common neoplasm of the brain. When these occur in the brainstem, prognosis is poor and treatment options are limited. However, stereotactic radiosurgery has been investigated as a management tool for brainstem metastases. The aim of this review is to gather and summarize data related to the safety and efficacy of stereotactic radiosurgery for the treatment of brainstem metastases. To identify trials for inclusion in this review, a PubMed search using the keywords "stereotactic radiosurgery" and "brainstem metastases" was performed. With this method, we selected 21 series published between 1999 and 2014. Median survival times for these studies averaged 8.3 months (range: 3-16.8 months). Control of systemic disease and performance status were identified as important predictors of survival time. Adjuvant whole-brain radiation therapy was not shown to increase survival. The studies reviewed here report adverse radiation effects at an average rate of 6.7% (range: 0-27%). Stereotactic radiosurgery provides effective local tumor control and may increase survival time for patients with brainstem metastases. Further study is needed to establish dosage guidelines for maximal benefit as well as to evaluate the efficacy of radiosurgery in symptom management.

Keywords: Brain; Brainstem; Gamma knife; Metastases; Stereotactic radiosurgery

Background

The most common intracranial neoplasms are metastases from other primary tumors, originating most frequently from lung, melanoma, renal, breast and colorectal cancers. Metastatic brain tumors occur in 10-30% of adult cancer patients. Metastatic lesions of the brainstem, accounting for 1.5 to 11% of all brain metastases, cause significant neurological deficit because of the dense concentration of neural tracts and nuclei in this structure, which are essential for normal function in this area [1]. Historically, estimated survival in these cases is between 1 and 6 months [2]. Distribution of metastatic disease is proportional to the relative blood flow of different areas of the brain [3,4] and accounts for the relative rarity of brainstem metastases. Surgical resection of these lesions is generally not an option, and chemotherapy is of limited utility.

In light of these limitations, Stereotactic Radiosurgery (SRS) and whole-brain radiation therapy (WBRT) have become important tools in the management of Brainstem metastases. Both Gamma Knife Radiosurgery (GKRS) and Linear Accelerator (LINAC) based SRS will be explored in this review. These procedures are minimally invasive and therefore ideally suited for treating Brainstem metastases. Further, they have the added benefits of being virtually painless and allowing most patients' rapid return to pre-treatment activities.

There is a rapidly growing body of literature regarding SRS treatment for Brainstem metastases; the goal of this review is to provide outcome data from these studies with special attention paid to optimizing patient selection for maximizing survival time and quality of life as well as identifying future directions for study of this technique. To identify trials for inclusion in this review, a PubMed search using the keywords "stereotactic radiosurgery" and "brainstem metastases" was performed. With this method, we selected 21 series inclusive of both Gamma Knife and linear accelerator based platforms published between 1999 and 2014.

Review

Tumor histology

Multiple studies have described which patients are more apt to develop brain metastases, but specific epidemiologic data on metastases in the brainstem is very limited. Yen et al. looked at 751 patients with brain metastases and found that while lung cancer was the most common source of metastases, breast cancer primary tumors had the highest incidence of brainstem involvement (12.4%) followed by ovarian (8.3%), renal cell carcinoma (8.2%), colorectal cancer (7.4%), lung cancer (5.5%), and melanoma (4.2%) [4].

SRS basic outcomes

Since 1999, there have been several studies of Gamma Knife radiosurgery (GKRS) [1,4-16] and linear accelerator based radiosurgery [17-22] treatment of Brainstem metastases. All of these have concluded that these technologies provide favorable local tumor control with minimal toxicity. Table 1 details the patient characteristics and

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Study	Year	Method	Number of patients/ Number of lesions treated	Mean KPS	Median Age	Patients with single metastasis (%)	Patients receiving concurrent/ previous WBRT (%)	Mean tumor volume (cm^3)	Median survival time (mos)	Mean marginal dose (Gy)	Local control (%)
Kilburn	2014	GK	44/52	80 (median)	57	25	57	0.134 (median)	6	18 (median)	82
Peterson	2014	GK	41/NR	NR	59 (median)	73	46	0.66	4.4	17	91
Jung	2013	GK	32/NR	NR	50	34	53	0.71	5.2	13 (median)	87.5
Sengoz	2013	GK	44/46	80 (median)	57	34	66	0.6	8	16 (median)	96
Kawabe	2012	GK	200/222	90 (median)	64 (mean)	93	7	1.3	6	18	82
Leeman	2012	LINAC	36/38	80 (median)	62	24	44	0.94 (median)	3	17	93
Li	2012	GK	28/32	80 (median)	61	18	0	0.783 (median)	9	16 (median)	90.6
Lin	2012	LINAC	45/48	80 (median)	60 (mean)	96	47	0.4 (median)	11.6	14 (median)	92
Yoo	2011	GK	32/NR	NR	56 (mean)	19	NR	1.5	7.7	15.9	87
Valery	2011	LINAC	30/43	80	57 (mean)	67	27	2.8 (median)	10	13.4	90
Hatiboglu	2011	LINAC	60/NR	90 (median)	61	NR	25	1.0 (median)	4.2	15.0 (median)	76
Kelly	2011	LINAC	24/NR	80 (median)	57	13	96	0.2 (median)	5.3	13	79
Koyfman	2010	GK	43/43	80 (median)	59	100	79	0.37 (median)	5.8	15.0 (median)	85
Samblas	2009	LINAC	28/30	NR	53 (mean)	46	96	1.86	16.8	11	NR
Lorenzoni	2009	GK	25/27	79	53	24	52	0.6	11.1	20	95
Kased	2008	GK	42/44	90 (median)	55	12	57	0.26 (median)	9	16.0 (median)	85
Hussain	2007	GK	22/25	92	60	86	14	0.90 (median)	8.5	16.0 (median)	100
Fuentes	2006	GK	28/NR	80	58 (mean)	71	21	2.1	12	19.6	92
Yen	2006	GK	53/NR	80	57 (mean)	36	40	2.8	11	17.6	NR
Shuto	2003	GK	25/31	NR	54	32	28	2.1	4.9	13	77
Huang	1999	GK	26/27	80	61	42	92	2	9	16.0 (median)	95

Abbreviations: NR - not reported, GK – Gamma Knife, LINAC – linear accelerator

Table 1: Patient characteristics, dose, and local control [1,2,4-6,8-22].

outcomes of these studies. All of these are retrospective studies and, with the exception of Kawabe et al. who had 200 patients, had relatively small sample sizes, ranging from 22 to 60. Median survival time (MST) for these studies averages 8.3 months (range 3-16.8 months).

Direct comparison of the systems used to perform SRS for brainstem metastases has not been performed, however dosimetric comparisons exist for treatment of meningiomas, arteriovenous malformations, and acoustic neuromas using Gamma Knife, Cyberknife, or the Novalis high-definition multileaf collimator system [23,24]. These studies found Gamma Knife and Cyberknife with their multiple focal entries provided superior conformity compared to the Novalis. Gamma knife was also shown to have the steepest dose gradient, thus exposing tissue surrounding lesions to the lowest radiation dose. Advantages of the Cyberknife and Novalis systems include shorter average beam-on time and image verification at the time of treatment. It should be noted, however, that this dosimetric data has not been shown to relate to clinical outcomes. Further, these data may not be applicable to brainstem lesions, and it is not clear which of the numerous variables involved in radiosurgery will be most impactful in the treatment of lesions in this highly eloquent area.

The wide range of survival times presented here calls for characterization of prognostic factors that influence patient outcomes. One of the retrospective studies reviewed here, a 2009 publication by Lorenzoni et al., analyzed the utility of three different stratification systems used for survival time estimation and patient selection. They compared the Radiation Therapy Group's Recursive Partitioning Analysis (RPA), the Score Index for Radiosurgery in Brain Metastases (SIR), and the Basic Score for Brain Metastases (BSBM). Multivariate analysis showed BSBM to be the strongest predictor of patient outcome (p=0.00015) [12]. Under this scoring system, patients receive one point for each of the following favorable conditions: KPS >80, primary tumor control, and absence of extra cranial disease. While only one other study reviewed here makes use of the BSBM [21], the patient characteristics used to calculate it were found individually or together to be significant predictors of survival by several of the other investigators (Table 2). Control of systemic disease and performance status, especially KPS, were the two factors most frequently found to be significant. Hatiboglu et al. and Kased et al. also found that patients with metastases from melanoma primary tumors had significantly worse outcomes (p=0.002 and p=0.003 respectively) [13,21].

Systemic disease control makes sense as an important factor contributing to outcomes especially when one considers the natural history of brainstem metastasis progression. In studies reporting cause of death, an average of only 5% (range 0-13%) of patients died from progression of their Brainstem metastases while 65% (range 42-89%) died from systemic disease, and 25% (range 7-43%) died from non-brainstem intracranial disease (Table 3). The studies with the shortest MSTs, Leeman et al. and Hatiboglu et al. with 3 and 4.2

Study	Year	increased survival time in multivariate analysis (p value)
Kilburn	2014	none found
Peterson	2014	KPS>80, absence of prior WBRT
Jung	2013	favorable RTOG RPA class, single metastasis
Sengoz	2013	none found
Kawabe	2012	favorable KPS (0.001), single metastasis (0.012), well controlled primary (0.021)
Leeman	2012	none found
LI	2012	NR
Lin	2012	none found
Yoo	2011	KPS > 70 (0.0001), RPA 1 or 2 (0.0014)
Valery	2011	none found
Hatiboglu	2011	smaller pre-SRS tumor volume (0.008), non-melanoma primary (0.002), no necrosis in pre-SRS MRI (0.04), female sex (0.03), BSBM 2-3 (0.007), SIR > 5 (0.003)
Kelly	2011	none found
Koyfman	2010	greater performance status (0.0009), smaller tumor volume (0.0128)
Samblas	2009	NR
Lorenzoni	2009	no WBRT (0.005), KPS > 80 (0.0025), primary tumor controlled (0.007), favorable BSBM (0.00015)
Kased	2008	single metastasis (0.003), non-melanoma primary (0.003), extracranial disease controlled (0.058)
Hussain	2007	NR
Fuentes	2006	NR
Yen	2006	limited systemic disease (0.0293)
Shuto	2003	NR
Huang	1999	no active extracranial systemic disease (0.0008)

Abbreviations: KPS – Karnofsky performance status, RPA – Radiation Therapy Oncology Group Recursive Partitioning Analysis score, NR – not reported

Table 2: Prognostic factors associated with longer median survival time [1,2,4-22].

months respectively both attribute their discrepant results to higher rates of active extracranial disease in their patients than in other studies reporting longer survival [18,21]. Samblas et al. had the longest MST and report that 85.7% of their patients had well-controlled primary tumors [22].

While Brainstem metastases are rarely the cause of death in these patients if they are treated, they frequently cause significant neurological deficit. The goal of SRS treatment of Brainstem metastases, therefore, should be preservation of functional status and improvement of existing symptoms. Kawabe et al. measured both quantitative and qualitative survival in their study participants. Patients with a higher KPS, single metastasis, and well-controlled primary tumors lived longer in this study while higher KPS and smaller tumor volume predicted longer qualitative survival which was defined as maintaining a KPS above 70 [1]. Improvement of brainstem related symptoms was reported in nearly half of these studies and averaged 41% (range 9-60%) (Table 4).

Adjuvant whole brain radiation therapy

Use of whole-brain radiation therapy prior to or concurrent with SRS occurred in all but two studies [9,10]. Lorenzoni et al. found that patients who did not receive WBRT had significantly longer survival than those who did [12], a finding which may be contributed to selection bias. Most recent data on the use of WBRT in combination with SRS for treatment of all brain metastases have shown no quantitative survival benefit from the combination over either therapy used alone. A 2012 Cochrane review by Patil et al. revealed improved performance status in terms of KPS and better local tumor control (HR 0.27; 95% CI 0.14 to 0.52) but overall survival was not significantly different for patients receiving WBRT plus SRS versus those who had WBRT alone [24]. Comparing SRS alone to combination therapy yields similar results. Aoyama et al. also did not find increased survival with WBRT plus SRS, but noted reduced recurrence of targeted tumors as well as fewer distant intracranial relapses requiring salvage treatment ($p<0.001$) [25].

Perhaps most relevant to brainstem metastasis patients specifically are emerging studies demonstrating the negative effect of WBRT on neurological function. Chang et al. found that four months after treatment, patients who had WBRT plus SRS have a greater risk of memory decline and learning abilities (mean posterior probability of decline =52%) when compared to SRS patients (mean posterior probability of decline =24%) [26]. Further, Soffietti et al. recently published results of a phase III trial comparing adjuvant WBRT to observation following surgery or radiosurgery for BMs. They found a significant decline in quality of life based on the Health Related Quality-of-Life (HRQOL) inventory at 9 months in patients who received WBRT ($p=0.0148$) [27]. The HRQOL used in this instance took into consideration global health status, physical, cognitive, role and emotional functioning, and fatigue. Given these data, a strategy of SRS treatment up front will not sacrifice survival and may delay or avoid neurocognitive side effects.

Adverse effects of SRS

While radiation based treatments have become mainstays in management of Brainstem metastases, it is important to consider the potential side effects associated with SRS. In an analysis of 279 radiosurgery procedures for brain metastases, Hong et al. found that 30 days post-procedure, less than 2% of patients experienced adverse events requiring hospitalization. 34.1% of these patients experienced acute sequelae but most of these were mild to moderate and included headache, seizures, and fluid retention [28]. Among the studies reviewed here, an average of 6.3% (range 0-27%) of patients experienced adverse effects; however this number may be low due to varied reporting methods between the studies. Some reported all effects no matter how transient or mild, while others reported only what they considered to be serious side effects. All reported complications are detailed in Table 5.

There is a long-standing belief that the brainstem is an especially radiosensitive structure, largely based on work by Boden et al. [29]. Today, no dosage guidelines exist for the treatment of Brainstem metastases with radiosurgery, so selection of doses in the reviewed studies is largely based on conservative estimates and previous work by other investigators. Yen et al. determined radiation dosage based on tumor volume and history of previous radiotherapy [4]. Marginal tumor dose in these studies ranges from 11 to 20 Gy, and it is difficult to observe trends in effectiveness in these series based on dose. Many factors are likely at play including tumor volume and use of adjuvant WBRT. Lorenzoni et al. found a correlation between tumor size and marginal dose. Tumors less than 0.2 ml in volume received mean marginal dose of 22.1 Gy, while larger lesions received a mean marginal dose of 17.6 Gy ($p<0.0001$) [12]. More recently, Kilburn et al. found higher rates of toxicity in patients with tumor size greater than 1.0 cc [6]. These findings relating exposure volume to toxicity make sense given earlier work by Voges et al. and Flickinger et al. who found that toxicity was significantly predicted by the volume of normal brain tissue exposed to a critical dose of radiation (10 and 12 Gy respectively) [30,31].

Study	Year	Number of patients with known cause of death	Deaths caused by BSM progression (%)	Deaths caused by systemic disease (%)	Deaths caused by non-BSM intracranial disease (%)	Other cause of death
Kilburn	2014	NR				
Peterson	2014	NR				
Jung	2013	NR				
Sengoz	2013	NR				
Kawabe	2012	175	2%	89%	9%	
Leeman	2012	20		60%		
LI	2012	28	4%	68%	29%	
Lin	2012	NR				
Yoo	2011	15	7%	60%	33%	
Valery	2011	19		58%		42% neurological relapse
Hatiboglu	2011		2%	71%	7%	
Kelly	2011	18	0%	83%	17%	
Koyfman	2010	NR				
Samblas	2009	24	4%	42%	43%	4% MI, 4% chemotherapy toxicity
Lorenzoni	2009	NR				
Kased	2008	19	5%	63%	32%	
Hussain	2007			55%	23%	22% unknown
Fuentes	2006	16	13%	50%	38%	
Yen	2006	43	7%	79%	14%	
Shuto	2003			NR		28% metastatic brain tumors
Huang	1999			NR		3 from new tumor growth, 1 new tumor + sys dz

Abbreviations: COD – cause of death

Table 3: Reported cause of death in study participants [1,2,4-22].

Study	Year	Patients presenting with symptoms who had improvement after GKRS (%)
Kilburn	2014	NR
Peterson	2014	NR
Jung	2013	32
Sengoz	2013	NR
Kawabe	2012	NR
Leeman	2012	NR
Li	2012	NR
Lin	2012	NR
Yoo	2011	NR
Valery	2011	57
Hatiboglu	2011	NR
Kelly	2011	50
Koyfman	2010	NR
Samblas	2009	42
Lorenzoni	2009	NR
Kased	2008	10
Hussain	2007	9
Fuentes	2006	57
Yen	2006	60
Shuto	2003	NR
Huang	1999	50

Abbreviations: NR – not reported

Table 4: Reported improvement of brainstem tumor-related symptoms [1,2,4-22].

Valery et al. used one of the lowest doses in this review at 13.4 Gy, but achieved local control of 90% and MST of 10 months, similar to results in the study with the highest dose by Lorenzoni et al. who used 20 Gy and report local control of 95% and MST of 11.1 months [19,12]. While it may be logical that minimizing dose would reduce the frequency of adverse effects, metastases in the brainstem could present special circumstances. Relatively shorter survival times among brainstem metastasis patients might mask late-appearing adverse effects. Interestingly, three of the four studies with the highest doses report zero adverse effects [4,12,2]. Further, doses of at least 20 Gy were significantly correlated with longer survival in the series by Leeman et al. [18].

Conclusions

Brainstem metastases are uncommon occurrences in the natural history of some cancers and carry a poor prognosis. They are usually unresponsive to chemotherapy and inaccessible with surgery. The studies reviewed here have established that stereotactic radiosurgery provides effective tumor control and may increase survival time in these patients with minimal adverse effects. They have also solidly established that performance status and systemic disease control are good predictors of prolonged overall survival.

These data support the use of SRS as a first line of treatment for Brainstem metastases. Since these studies show that systemic disease or non-brainstem intracranial disease are the cause of death much more often than Brainstem metastases themselves, we believe that future studies should focus on the effects of SRS on quality of life and symptom management as well as the role of WBRT versus SRS alone for primary management. The HRQOL used by Soffietti et al. could be of

Study	Year	Number of treatment related complications (percent)	Type of complication, number of each
Kilburn	2014	4 (9%)	1 brainstem necrosis, 1 disequilibrium, 1 hemiparesis, 1 facial numbness with hemiparesis
Peterson	2014	1 (2%)	1 fatal brain hemorrhage
Jung	2013	0	
Sengoz	2013	2 (4%)	2 asymptomatic peritumoral image changes
Kawabe	2012	7 (4%)	7 peritumoral edema (1 severe)
Leeman	2012	3 (8%)	1 nausea, 2 headache
LI	2012	1 (4%)	1 peritumoral edema
Lin	2012	2 (4%)	1 radionecrosis, 1 facial palsy
Yoo	2011	1 (3%)	1 pontine hemorrhage
Valery	2011	4 (13%)	4 headache controlled with corticosteroids
Hatiboglu	2011	12 (20%)	4 hemiparesis, 2 cranial nerve deficits, 3 headache, 4 nausea/vomiting, 2 peritumoral hemorrhage
Kelly	2011	2 (8%)	1 ataxia, 1 confusion
Koyfman	2010	5 (12%)	2 radionecrosis, 1 weakness, 1 ataxia, 1 pin-site bleed
Samblas	2009	0	
Lorenzoni	2009	0	
Kased	2008	4 (10%)	2 radionecrosis, 1 hemiparesis, 1 pontine hemorrhage
Hussain	2007	1 (5%)	1 hemiparesis
Fuentes	2006	0	
Yen	2006	0	
Shuto	2003	2 (8%)	2 peritumoral edema
Huang	1999	7 (27%)	4 nausea/vomiting, 3 seizures

Table 5: Treatment associated complications [1,2,4-22].

particular value if used to study brainstem metastases specifically since this inventory gives a more complete picture of patient benefits than survival time alone.

Retrospective design and relatively small size limit all of the studies presented here. Further, since brain stem metastases are rare, collecting data on these cases takes several years during which many practices will likely have undergone transition to electronic medical records which means information collected is severely limited by availability of patient demographic and treatment data. For example, while average marginal dose is the radiation exposure parameter used by all of these studies, other measures such as conformity index, maximum target dose, or planned target volume may give more accurate information for drawing conclusions about safety and efficacy of SRS. These measures are readily calculated by newer treatment planning systems, which should allow future studies to provide a more complete picture of the effects of SRS treatment.

As these better parameters become more readily available to investigators, future studies will likely be able to establish clear dose guidelines for these treatment techniques. While these data suggest that higher doses are safe, it remains unclear whether they truly enhance survival time and tumor control. More specific information regarding treatment parameters will also help identify how variations in treatment affect clinical outcomes including possibly identifying thresholds for WBRT or fractionation. Additionally, as SRS treatment for Brainstem metastases becomes a mainstay, investigation of outcomes in salvage treatments for patients who have local failure should be characterized.

Our current approach is upfront SRS in patients with solitary or limited Brainstem metastases. We generally reserve WBRT for later salvage of more disseminated intracranial disease. If patients present with multiple brain or brainstem metastases we usually use WBRT with SRS boost. We recommend at least 16 Gy for SRS alone depending on tumor size and histology and 16 Gy or less for SRS when used in combination with WBRT of 3750 cGy.

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References

1. Kawabe T, Yamamoto M, Sato Y, Barfod BE, Urakawa Y, et al. (2012) Gamma Knife surgery for patients with brainstem metastases. J Neurosurg 117 Suppl: 23-30.
2. Fuentes S, Delsanti C, Metellus P, Peragut JC, Grisoli F, et al. (2006) Brainstem metastases: management using gamma knife radiosurgery. Neurosurgery 58: 37-42.
3. Delattre JY, Krol G, Thaler HT, Posner JB (1988) Distribution of brain metastases. Arch Neurol 45: 741-744.
4. Yen CP, Sheehan J, Patterson G, Steiner L (2006) Gamma knife surgery for metastatic brainstem tumors. J Neurosurg 105: 213-219.
5. Peterson HE, Larson EW, Fairbanks RK, MacKay AR, Lamoreaux WT, et al. (2014) Gamma knife treatment of brainstem metastases. Int J Mol Sci 15: 9748-9761.
6. Kilburn JM, Ellis TL, Lovato JF, Urbanic JJ, Daniel Bourland J, et al. (2014) Local control and toxicity outcomes in brainstem metastases treated with single fraction radiosurgery: is there a volume threshold for toxicity? J Neurooncol 117: 167-174.
7. Sengöz M, Kabalay IA, TezcanlÄ E, Peker S, Pamir N (2013) Treatment of brainstem metastases with gamma-knife radiosurgery. J Neurooncol 113: 33-38.
8. Jung EW, Rakowski JT, Delly F, Jagannathan J, Konski AA, et al. (2013) Gamma Knife radiosurgery in the management of brainstem metastases. Clin Neurol Neurosurg 115: 2023-2028.
9. Li Y, Xu D, Zhang Z, Zhang Y, Liu D, et al. (2012) Gamma Knife surgery for brainstem metastases. J Neurosurg 117 Suppl: 13-16.
10. Yoo TW, Park ES, Kwon do H, Kim CJ (2011) Gamma knife radiosurgery for brainstem metastasis. J Korean Neurosurg Soc 50: 299-303.
11. Koyfman SA, Tendulkar RD, Chao ST, Vogelbaum MA, Barnett GH, et al. (2010) Stereotactic radiosurgery for single brainstem metastases: the cleveland clinic experience. Int J Radiat Oncol Biol Phys 78: 409-414.
12. Lorenzoni JG, Devriendt D, Massager N, Desmedt F, Simon S, et al. (2009) Brain stem metastases treated with radiosurgery: prognostic factors of survival and life expectancy estimation. Surg Neurol 71: 188-195.
13. Kased N, Huang K, Nakamura JL, Sahgal A, Larson DA, et al. (2008) Gamma knife radiosurgery for brainstem metastases: the UCSF experience. J Neurooncol 86: 195-205.
14. Hussain A, Brown PD, Stafford SL, Pollock BE (2007) Stereotactic radiosurgery for brainstem metastases: Survival, tumor control, and patient outcomes. Int J Radiat Oncol Biol Phys 67: 521-524.
15. Shuto T, Fujino H, Asada H, Inomori S, Nagano H (2003) Gamma knife radiosurgery for metastatic tumours in the brain stem. Acta Neurochir (Wien) 145: 755-760.
16. Huang CF, Kondziolka D, Flickinger JC, Lunsford LD (1999) Stereotactic radiosurgery for brainstem metastases. J Neurosurg 91: 563-568.

17. Lin CS, Selch MT, Lee SP, Wu JK, Xiao F, et al. (2012) Accelerator-based stereotactic radiosurgery for brainstem metastases. Neurosurgery 70: 953-958.
18. Leeman JE, Clump DA, Wegner RE, Heron DE, Burton SA, et al. (2012) Prescription dose and fractionation predict improved survival after stereotactic radiotherapy for brainstem metastases. Radiat Oncol 7:107.
19. Valery CA, Boskos C, Boisserie G, Lamproglou I, Cornu P, et al. (2011) Minimized doses for linear accelerator radiosurgery of brainstem metastasis. Int J Radiat Oncol Biol Phys 80: 362-368.
20. Kelly PJ, Lin YB, Yu AY, Ropper AE, Nguyen PL, et al. (2011) Linear accelerator-based stereotactic radiosurgery for brainstem metastases: the Dana-Farber/Brigham and Women's Cancer Center experience. J Neurooncol 104: 553-557.
21. Hatiboglu MA, Chang EL, Suki D, Sawaya R, Wildrick DM, Weinberg JS (2011) Outcomes and prognostic factors for patients with brainstem metastases undergoing stereotactic radiosurgery. Neurosurgery 69 (4): 796-806.
22. Samblas JM, Sallabanda K, Bustos JC, Gutierrez-Diaz JA, Peraza C, et al. (2009) Radiosurgery and whole brain therapy in the treatment of brainstem metastases. Clin Transl Oncol 11: 677-680.
23. Gevaert T, Levivier M, Lacornerie T, Verellen D, Engels B, et al. (2013) Dosimetric comparison of different treatment modalities for stereotactic radiosurgery of arteriovenous malformations and acoustic neuromas. Radiother Oncol 106: 192-197.
24. Kaul D, Badakhshi H, Gevaert T, Pasemann D, Budach V, eta l. (2015) Dosimetric comparison of different treatment modalities for stereotactic radiosurgery of meningioma. Acta neurochirurgica 157: 559-563.
25. Patil CG, Pricola K, Sarmiento JM, Garg SK, Bryant A, et al. (2012) Whole brain radiation therapy (WBRT) alone versus WBRT and radiosurgery for the treatment of brain metastases. Cochrane Database Syst Rev 9: CD006121.
26. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, et al. (2006) Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA 295: 2483-2491.
27. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF et al. (2009) Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol 10: 1037-1044.
28. Soffietti R, Kocher M, Abacioglu UM, Villa S, Fauchon F, et al. (2013) A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results. J Clin Oncol 31: 65-72.
29. Hong T, Tome W, Hayes L, Yuan Z, Badie B, et al. (2004) Acute Sequelae of Stereotactic Radiosurgery, Radiosurgery. Karger.
30. Boden G (1948) Radiation myelitis of the cervical spinal cord. Br J Radiol 21: 464-469.
31. Flickinger JC, Kondziolka D, Lunsford LD, Kassam A, Phuong LK, et al. (2000) Development of a model to predict permanent symptomatic postradiosurgery injury for arteriovenous malformation patients. Arteriovenous Malformation Radiosurgery Study Group. Int J Radiat Oncol Biol Phys 46: 1143-1148.
32. Voges J, Treuer H, Sturm V, Büchner C, Lehrke R, et al. (1996) Risk analysis of linear accelerator radiosurgery. Int J Radiat Oncol Biol Phys 36: 1055-1063.