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. Adjunct 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 10-30% of adult cancer patients. Metastatic brainstem 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 (5.3%), 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 treatment outcomes for the included studies.

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 (5.3%), and melanoma (4.2%) [4].

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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.

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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 directly to clinical outcomes. Further, these data may not be applicable to 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
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. Ayama 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 Yoges 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].
Table 3: Reported cause of death in study participants [1,2,4-22].

| 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                                          | 2%                                  | 89%                                  | 9%                                               |                     |
| Peterson   | 2014 | NR                                          | 4%                                  | 68%                                  | 29%                                              |                     |
| Jung       | 2013 | NR                                          | 7%                                  | 60%                                  | 33%                                              |                     |
| Sengoz     | 2013 | NR                                          | 58%                                 |                                       | 42% neurological relapse                         |                     |
| Kawabe     | 2012 | 175                                         | 2%                                  | 71%                                  | 7%                                               |                     |
| Leeman     | 2012 | 20                                          | 4%                                  | 68%                                  | 29%                                              |                     |
| Li         | 2012 | NR                                          | 4%                                  | 60%                                  | 33%                                              |                     |
| Lin        | 2012 | NR                                          | 7%                                  | 60%                                  | 33%                                              |                     |
| Yoo        | 2011 | 15                                          | 58%                                 |                                       | 42% neurological relapse                         |                     |
| Valery     | 2011 | 19                                          | 2%                                  | 71%                                  | 7%                                               |                     |
| Hatiboglu  | 2011 | 19                                          | 5%                                  | 63%                                  | 32%                                              |                     |
| Kelly      | 2011 | 18                                          | 0%                                  | 83%                                  | 17%                                              |                     |
| Koyfman    | 2010 | NR                                          | 13%                                 | 50%                                  | 38%                                              |                     |
| Samblas    | 2009 | 24                                          | 4%                                  | 42%                                  | 43%                                              |                     |
| Lorenzoni  | 2009 | NR                                          | 7%                                  | 79%                                  | 14%                                              |                     |
| Kased      | 2008 | 19                                          | 5%                                  | 63%                                  | 32%                                              |                     |
| Hussain    | 2007 | 16                                          | 13%                                 | 50%                                  | 38%                                              |                     |
| Fuentes    | 2006 | 43                                          | 7%                                  | 79%                                  | 14%                                              |                     |
| Yen        | 2006 | NR                                          | 9%                                  | 71%                                  | 22% unknown                                      |                     |
| Shuto      | 2003 | NR                                          | 7%                                  | 79%                                  | 14%                                              |                     |
| Huang      | 1999 | NR                                          | 9%                                  | 71%                                  | 22% unknown                                      |                     |

Abbreviations: COD – cause of death

Table 4: Reported improvement of brainstem tumor-related symptoms [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

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

| 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 pituitary 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         |

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