Radiosurgery for Brain Metastases

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Introduction

Except for solitary lesions causing mass effect, the treatment of brain metastases is primarily palliative. In the case of solitary metastases, the occurrence of long-term survival is not unheard of; but in general, the guiding philosophy is palliation, reversal of neurologic deficits and maintenance of quality of life and functional status. There has been disagreement regarding the total number and volume of tumors which can be treated using Gamma Knife radiosurgery in the instance of multiple metastases. Published data from many groups have suggested that more than 3 lesions should be treated using whole brain radiotherapy. However, we have experience successfully treating more than this number of tumors using radiosurgery alone in one or multiple sessions.

Surgical extirpation of a solitary brain metastasis has been shown to significantly prolong survival if the primary disease is controlled. Likewise, whole-brain irradiation has been shown to be of benefit for certain tumor subtypes. These conclusions and the well-defined margins of most metastatic lesions on neuroimaging studies make them amenable to GKS. Because of the high incidence of these lesions, the treatment of metastatic tumors has become one of the most common indications for GKS worldwide.

Application of Radiosurgery for Brain Metastases

Radiobiological Principles

Brain metastases are suited for radiosurgery because of their relatively small size and discrete margin on magnetic resonance (MR)-imaging. The growth characteristics, oxygenation, and mitotic activity of metastasis in the brain are all major factors in determining the biological effectiveness of radiosurgery in treating metastatic disease and are reviewed in this section.

Early in the era of clinical radiotherapy, it was observed that multiple treatments (fractions) with reduced doses per fraction improved the therapeutic ratio when treating malignant tumors. However, with brain metastasis, it became clear that additional radiation beyond that of the traditional 30Gy in 10 fractions was required to achieve a lasting cure of the metastatic cancer to the brain. Such additional radiation dose could not be delivered using conventional fractionation techniques without substantially increasing toxicity to the surrounding brain tissue.

The delivery of an inhomogeneous dose to the treatment field with a higher dose at the center of a tumor (the so-called hot spot) may be desirable for several reasons in the treatment of metastatic tumors. First, it offsets the relative protection offered by the poor oxygenation of the tumor core; second, it increases the cell kill in the tumor cells adjacent to those in the hot spots due to the fact that the effect of a given dose to a population of cells is more damaging if the neighboring cells receive a high dose.(28, 29)

Technical Considerations

Radiosurgical dosing is usually described in terms of the amount of radiation delivered to the tumor margin. This allows an understanding of the minimum amount of radiation delivered to every tumor cell. Because of dose-volume constraints in radiosurgery, lower doses are generally delivered to larger tumors. Such lower doses may affect the control rate of the tumor.
Dose escalation studies were evaluated by the Radiation Therapy Oncology Group (RTOG) in study 95-05.(56, 57) This study looked at patients who failed prior conventional radiation therapy. Patients had either a brain metastasis or a primary brain tumor; patients with tumors in the brainstem were excluded. The dose escalation protocol was stratified by lesion diameter. Beginning with margin doses of 18, 15, and 12 Gy for tumors with diameters of 20, 21-30, and 31-40 mm respectively, doses were escalated in 3 Gy intervals in successive cohorts until unacceptably high toxicity (defined as greater than 30%) was reached. The patient cohort with tumors of 20 mm or less never exceeded 30% grade 3 toxicity at 24 Gy and researchers refused to escalate the dose any higher.

Radiosurgery in the management of brain metastases

A Review of the Literature

Radiosurgery has been used to treat patients with metastastic cancer to the brain. Radiosensitive tumor histologies such as nonsmall cell lung cancer and breast cancer respond well to stereotactic radiosurgery.

Somewhat surprisingly, radiation resistant tumor histologies such as melanoma and renal cell carcinoma respond quite well to radiosurgery as well.(6, 9, 10, 13, 27, 31, 35, 47, 51, 62) We briefly review the radiosurgical literature by tumor histology. Nonsmall cell lung cancer; Lung cancer is the leading cause of death from cancer and the most common source of brain metastases. Depending on the actual histological subtypes, lung carcinoma metastasizes intracranially between 13 and 54% of the time. The overall frequency of brain metastasis in patients with lung carcinoma is approximately 32% and between 54 and 64% of patients with lung carcinoma metastatic to the brain harbor or eventually develop multiple lesions.(8, 17) Although WBRT is frequently used prophylactically for small cell lung cancer patients, radiosurgery is frequently employed for patients with nonsmall cell lung cancer metastatic to the brain.

Sheehan et al reported an overall median patient survival time of 15 months (range 1–116 months) from the diagnosis of brain metastases and 7 months from radiosurgery in a series of 273 patients with brain metastases from nonsmall cell carcinoma.(59)

High preoperative KPS score, small tumor volume, absence of active systemic disease, long duration between diagnosis of lung carcinoma and the development of brain metastasis, frontal lobe location, and adenocarcinoma subtype correlated with favorable survival. Postradiosurgical imaging revealed that 60% of the tumors decreased, 24% remained stable, and 16% eventually increased in size. In another series of 27 patients with brain metastases from small cell carcinoma who had shown intracranial disease despite WBRT, the overall median survival was 18 months from diagnosis of brain metastasis and 4.5 months from radiosurgery.(58) Local tumor control was achieved in 81% of tumors. Historically, patients with lung carcinoma brain metastases frequently died as a result of intracranial disease progression; however, 69.6% of patients with non-small cell and 41% of the patients with small cell lung carcinoma in the above-mentioned series died of extracranial disease progression or with known active systemic disease. In our experience, radiosurgery was able to control 90% of tumor with a prolonged survival of 14 months after Gamma knife radiosurgery.(42)

Table 1: Summary of select series using radiosurgery for lung cancer metastases to the brain.

<u>Breast Cancer:</u> While improved neuroimaging enabled early diagnosis of brain metastases, better treatment of systemic disease increased the frequency of the diagnosis of intracranial metastases. Through improved local and systemic treatments, breast cancer is one such cancer for which there has been prolonged survival and greater at risk years of developing brain metastasis. The advent of an effective targeted therapy, such monoclonal antibody against HER-2, allows patients to survive much longer than before, thus increased likelihood of central nervous system relapse.

Breast cancer is the second most common source for cerebral metastases. Incidences of metastasis to the central nervous system ranging from 10% to 20% have been reported in clinical series and 30% in autopsy series.(18, 66) Breast cancer is considered to be a relatively radiosensitive tumor and radiosurgery in the treatment of breast carcinoma that has metastasized to the brain has shown its effectiveness in prolonging overall survival. Gamma Knife surgery resulted in a median survival of 13 months from the date of radiosurgery in our experience.(25) Firlik et al reported a median survival time of 13 months after treatment.(23) Akyurek et al reported a 19-month median duration of survival after treatment.(1) High KPS, high score index for radiosurgery, small tumor volume, single metastases and age over 60 were reported to correlate with a longer survival. The tumor control rate from these studies ranged from 81 to 94%.

Table 2: Summary of select series using radiosurgery for breast cancer metastases to the brain.

<u>Melanoma:</u> The incidence of melanoma has progressively risen over the decades. Melanoma is now the third most common primary tumor associated with central nervous system metastasis. Brain metastases were found in up to 75% of melanoma cases at autopsy and involvement of the central nervous system is the cause of the death in approximately one third of all patients.(2) The median survival time for untreated patients with brain melanoma metastases is estimated to be less than 1 month. According to Sampson et al, survival can be prolonged up to 2 months by the use of corticosteroids.(52) Melanoma as well as renal cell carcinoma and sarcoma have been considered as radioresistant tumors. In fact, studies have shown marginal at best utility to WBRT in patients with melanoma metastases.(11, 12, 15, 20, 22, 24, 34, 65)

With a single high radiosurgical dose, the tumor control rate following radiosurgery for cerebral metastatic melanoma seems favorable ranging from 61 to 90%.(37, 49, 55, 68) However, the prolongation of survival was not promising with most series reporting median survival in the range of 5.7 to 7.1 months.(37, 49, 55, 68) The series from the University of Virginia showed a slightly longer survival of 10.4 months. (38) Solitary lesion, small tumor volume and absence of systemic disease were reported prognostic factors associated with good outcome. Radiosurgery seems to overcome the problem of radioresistance observed in melanoma.

Table 3: Summary of select series using radiosurgery for melanoma metastases to the brain.

<u>Renal Cell Carcinoma:</u> Renal cell carcinomas are responsible for approximately 2% of cancer deaths in the United States annually, and they have an 10% incidence of developing into brain metastases.(26) The resistance to fractionated radiation therapy and a tendency for limited numbers of metastases make radiosurgery a rationale alternative in the management of renal cell carcinoma metastases to the brain. The reported tumor control rate following radiosurgery for metastatic renal cell carcinoma ranged from 83 to 96%.(40, 46, 60, 61) The reported survival ranged from 8 to 15 months.(26, 39, 40, 46, 54, 60, 67) Low number of metastases, high KPS, high recursive partitioning analysis class, increased interval from primary to brain metastasis, small tumor volume and inactive systemic disease were associated with favorable survival.(39, 46, 54, 60)

Table 4: Summary of select series using radiosurgery for renal cell carcinoma metastases to the brain.

Efficacy when compared with WBRT alone

Whole brain radiation therapy is a widely accepted treatment modality for brain metastases. From a dismal average survival of 1 to 2 months without treatment, the combination of WBRT and surgery improves patient survival to an average of 3 to 6 months.(7, 36) Typically WBRT is administered using 30 Gy delivered in 10 fractions, although considerable variations may exist between protocols.(14) An RTOG study using hyperfractionation demonstrated improved survival and neurological function,(21) but a follow-up randomized trial in which patients received 1.6Gy twice a day and 54.4 Gy total could not conclusively show improved survival.(41)

Aoyama and colleagues published one of the only randomized controlled trials, studying 132 patients with up to four metastases each who underwent radiosurgery or radiosurgery followed by WBRT.(4) The primary end point was survival, with secondary end points including functional preservation and radiation toxicity. The Mini Mental Status Examination was used for assessment. The local recurrence rate in patients who received radiosurgery alone in this study was 76.4%, compared with 38.5% in the group that received WBRT and radiosurgery. In spite of this, patients who received radiosurgery alone did not have significant decreases in length of survival (7.5 months vs. 8 months) or in functional independence.

Deinsbeger et al.(16) studied 110 patients with new brain metastases and found a local control rate of radiosurgery without WBRT of 89.4% and a median survival of 12.5 months. Based on this high rate of control with the single modality, they recommended that WBRT be reserved for cases of numerous metastases or used in a delayed fashion for recurrence.

In our recently published data, we found that repeat radiosurgery was as effective as WBRT in the management of both synchronous and metachronous metastases in patients undergoing treatment for brain metastases.(30) Furthermore, patients who underwent radiosurgical treatment tended to have significantly higher KPS than those who received WBRT. This begs the question as to whether it would be prudent to use radiosurgery alone in patients with limited intracranial disease and high presentation performance status, followed by WBRT in the event of a treatment failure.

Radiosurgery with WBRT

In addition to the Aoyama study, two other randomized studies attempted to gauge the efficacy of WBRT and radiosurgery together. Kondziolka and colleague studied 27 patients (14 with WBRT alone and 13 who received WBRT in combination with radiosurgery and observed no significant difference in survival, although patients who received WBRT and radiosurgery did tend to live longer (11months vs. 7.5 months; p=0.26) and tended to have better control of brain disease.(32) Many criticisms have been levied against this study, including its relatively small patient size, and the fact that the trial closed early.

In a subsequent study, RTOG conducted a prospective randomized trial (RTOG 9508) of WBRT versus WBRT plus radiosurgery for patients with 1-3 brain metastases. In this study, WBRT plus radiosurgery conferred a survival advantage compared to WBRT alone (6.5 months vs. 4.9 months; $p<0.05$) in the following patient categories: i) solitary brain metastases (for which the study was stratified) and the following subsets ii) 1-3 metastases and RPA class I; iii) 1-3 metastases and age less than 50 years and; iv) 1-3 metastases and nonsmall cell lung cancer or any squamous carcinomas.(3)

Additionally, all subsets of patients in the WBRT plus radiosurgery group were more likely to have a stable or improved performance status, improved local control and reduced steroid dependence compared to the WBRT alone group. Systemic disease remained the primary cause of death (more than 66%) in both groups. Toxicities and the rate of re-operation were comparable in the two groups. Re-operation pathology showed necrosis in all patients in the WBRT plus radiosurgery arm and viable tumor in all patients in the WBRT arm.(3) In spite of this data, there is a considerable amount of conflict on how much benefited WBRT adds to radiosurgery. In the Patchell studies in which patients with a single brain metastasis were randomized to surgery alone vs. surgery followed by WBRT, the patients in the WBRT group were less likely to die of neurologic causes than patients in the observation group (14% vs. 44%, $p = 0.003$).(43-45) This is despite the fact that among the 70% of patients in the observation group who experienced a brain tumor recurrence, 88% received salvage WBRT either alone or in combination with surgery or radiosurgery.

A more recent report from the University of Kentucky shows that despite the use of high resolution treatment planning and every 3 month follow-up MRI in patients with newly diagnosed brain metastases, use of radiosurgery alone is associated with an increasing risk of brain recurrence with increasing survival time. In addition, the majority of such recurrences are symptomatic and associated with a neurologic deficit.(50)

However, in many of these patients, salvage radiosurgery can be used to treat these new metastases before they become symptomatic. In a study at UCSF, radiosurgery alone resulted in equivalent survival and intracranial control when compared to radiosurgery and WBRT for patients with one to four brain metastases.(63) In this retrospective report 62 patients treated with radiosurgery alone were compared to 43 treated with both modalities. Survival was 11.3 and 11.1 months, respectively. Remote failure was higher in the radiosurgery group (72 vs. 31%), but high successful salvage resulted in intracranial control 62 and 73% (not significantly different), respectively. It should be noted that selection bias was acknowledged and evident as there was a statistically significant greater number of patients with solitary metastases in the radiosurgery alone arm.

The natural history of intracranial disease in brain metastasis patients varies tremendously; predicting those that will have rapid versus slow progression is challenging at initial presentation. The identification of patients with different risk of developing brain tumor relapse could be extremely important to define the most appropriate initial management. Sawrie et al.(53) retrospectively analyzed 100 patients treated with radiosurgery alone to identify predictors of distant brain failure (DBF). Patients with fewer than four metastases, absent extracranial disease, and without melanoma histologic characteristics had a significant lower risk of DBF: median time to DBF and 1-year actuarial freedom from DBF for the low-risk subgroup were 89 weeks and 83%, respectively compared with 33 weeks and 26% for the high-risk subgroup. Other issues, which remain to be clarified, are the optimal schedule of WBRT when combined with radiosurgery and the usefulness of an assessment of minimal residual tumor after surgery with biological imaging (i.e. with PET).(5)

Radiosurgery following resection

The idea behind radiosurgery to the resection cavity stemmed from the landmark studies of Patchell and colleagues, who found the local recurrence of metastatic brain tumors to be as high as 46% in the absence of post-operative radiotherapy.(45) A number of reports have indicated that focused radiation to the resection cavity may be beneficial in terms of controlling tumor growth. (30, 33, 64)

Do and colleagues recently reported on 30 patients who underwent radiosurgery of the resection cavity, with 4 patients (13%) developing local recurrence at follow-up. The actuarial 12-month survival rate in this series was 82% for local recurrence-free survival and 67% for neurological deficit-free survival and 31% in terms of controlling new distant intracranial metastases.(19)

Quigley et al.(48) retrospectively reviewed 31 patients with up to four intracranial metastases treated with resection followed by radiosrgery to the resection cavity or radiosurgery alone. The lesions were less than 3 cc, and the median dose was 16 Gy. The mean survival was better for the patients who had undergone resection plus radiosurgery at 19.6 months than for those treated with radiosurgery alone at 10.3 months. Lesions treated with surgery and a radiosurgery boost had a local failure rate of 5.8%, and over 70% of the patients studied were spared the toxicity of WBRT.

Our experience is similar to the results reported above.(30) In 47 patients treated at the University of Virginia (mean prescription dose of 19.5 Gy), we found that local control was achieved in 94% of patients. Tumor recurrence at the surgical site was statistically only related to large tumor volume (all treatment failures had a treated volume of greater than 15 cm3 while the mean treatment volume for remaining patients was 9.9 cm3).
Seventy percent of patients in our series were managed using radiosurgery alone, although it is worth noting that patients who avoided WBRT tended to have lower tumor burden from the onset.

In cases where the resection cavity is targeted, most groups advocate the use of a 1-3mm margin around the cavity, with the idea of targeting any metastatic extension which may be at the periphery of the surgical field after what appears to be a complete resection. In their study of 76 resection cavities targeted using radiosurgery, Soltys et al.(64) tested the effectiveness of this strategy, and found that the local failure rate was most significantly correlated with lack of conformality in the treated field. Local tumor control was 100% for the least conformal quartile of patients, compared with only 63% for all remaining quartiles.

The effectiveness of radiosurgery to the tumor cavity is likely to be affected by the timing of radiosurgery following open surgery, although no study to date has examined this variable. Immediately performing radiosurgical treatment may face the difficulty of differentiating residual tumors from post-surgical neuro-imaging changes. As such, we generally wait for a period of 2-3 weeks before performing radiosurgery.

Conclusion

WBRT and resection continue to play a role in the management of patients with brain metastasis. Nevertheless, radiosurgery has emerged as a valuable tool in the management of patients with brain metastases. Survival and quality of life outcomes following radiosurgery appear to depend on variables such as tumor pathology, size, number of lesions, extent of systemic disease, and neurological performance at presentation.

Tables

Table 1: Summary of select series using radiosurgery for lung cancer metastases to the brain.

	Patients/tumor No	Prescription Dose (mean) (Gy)	Imaging Follow-up (mean/range) (months)	% with tumor control	Survival (mean) (months)	Factors associated with prolonged survival
Sheehan (2002)[1]	273/627	11-22.5 (16)	NS	84	7	Female Higher KPS Adenocarcinoma Absence of active systemic disease ↓ Interval from primary to brain metastases
Jawahar (2004)[2]	44/91	11-22 (15.4)	18.3	73	4.5	Controlled primary Good response to radiosurgery
UVA (2005)[2]	171/424	18-24 SRS and 14-18 SRS after WBRT	6 (3-63)	80.5 (159 lesions)	14	KPS ≥ 70 Age < 65 Margin dose > 14 Gy No cyst associated with the tumor Tumor volume < 2cm^3

1: non-small cell lung carcinoma only; 2: small and non-small cell lung carcinoma; 3: small cell lung carcinoma only

Table 2: Summary of select series using radiosurgery for breast cancer metastases to the brain.

	Patients/tumor No	Prescription Dose (mean) (Gy)	Imaging Follow-up (mean/range) (months)	% with tumor control	Survival (mean) (months)	Factors associated with prolonged survival
Firlik (2000)	30/58	12-20	9 (1-31)	93#	13	Solitary metastasis Small lesion (<4cm)
Amendola (2000)	68/518	15-24	NS	94#	7.8	NS
Lederman* (2001)	60/246	12-25 (1 fraction) 6 (4 fractions)	NS	82#	7.5	Solitary metastasis Absence of visceral diseases
Akyurek (2007)	49/84	14-20 (18)	NS	78% at 1 year 48% at 2 years	19	High KPS High SIR Postmenopausal status Positive estrogen receptor
UVA (2005)	43/84	NS	NS	71#	13	High KPS High SIR Patient age>60 years Solitary metastasis

71% had fractionated radiosurgery (4x600cGy); # based on the last image follow-up; SIR: Score Index for Radiosurgery

Table 3: Summary of select series using radiosurgery for melanoma metastases to the brain.

	Patients/tumor No	Prescription Dose (mean) (Gy)	Imaging Follow-up (mean/range) (months)	% with tumor control	Survival (mean) (months)	Factors associated with prolonged survival
Mathieu (2008)	244/754	10-22 (18)	8.1 (0.3-114.3)	86.2#	5.3	Solitary metastasis Small lesion (<8cm3) Absence of active systemic disease Non-cerebellar lesions
Christopoulou (2006)	29/105	15-30 (25.3)	NS	61#	5.7	Decreased numbers $ interval from primary to brain metastases
Radbill (2004)	51/188	10-21 (17.3)	NS	81#	6.1	RPA class 1 Solitary metastasis

						Non-cerebellar lesions
Selek (2004)	103/153	10-24 (18)	NS	49% at 1 year	6.7	High SIR
Yu (2002)	122/332	14-24 (20)	6.8	90#	7.0	Total tumor volume <3 cm^3 Inactive systemic disease

RPA: recursive partitioning analysis; SIR: Score Index for Radiosurgery; # based on the last image follow-up

Table 4: Summary of select series using radiosurgery for renal cell carcinoma metastases to the brain.

	Patients/tumor No	Prescription Dose (mean) (Gy)	Imaging Follow-up (mean/range) (months)	% with tumor control	Survival (mean) (months)	Factors associated with prolonged survival
Shuto (2006)	69/314	8-30 (21.8)	7.1 (3-39)	82.8	9.5	Low number of metastases High KPS High RPA class
Muacevic (2004)	85/376	(21)	NS	94	11.1	KPS > 70 RPA class I
Sheehan (2003)	69/146	12.5-20 (16)	NS	96	15	younger patient age High KPS 2 months from primary to brain metastases Higher marginal dose Higher maximal dose Higher treatment isodose
Hoshi (2002)	42/113	20-30 (25)	0.2-88 (12.5)	93	12.5	KPS≥80 Treated by GK more than once Obtained complete/partial response GK
Goyal (2000)	29/66	7-24 (18)	NS	91	10	None
UVA (2000)	21/37	10.5-40 (20)	14.5 (3-63)	100	8	None

71% had fractionated radiosurgery (4x600cGy); # based on the last image follow-up; SIR: Score Index for Radiosurgery

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