Evidence–Based Medicine for Gamma Knife® Radiosurgery

Photos courtesy of Jean Régis, Timone University Hospital, Marseille, France
Brain Metastases

Introduction
At least 12-13% of cancer patients develop symptomatic brain metastases (BM) and this figure is likely to rise as diagnostic technologies improve, allowing more occurrences to be identified. Further, increased survival time of cancer patients plays an important role. With no treatment, patients with symptomatic brain metastases usually die within two months of diagnosis. An early diagnosis and vigorous treatment of the brain metastasis, while only rarely curative, may lead to a useful remission of the neurological symptoms and may both enhance the quality of a patient’s life and prolong survival.

Brain metastases most often arise from lung (50%) or breast cancers. Other primary tumors that metastasize to the brain include melanoma, sarcomas and tumors arising in the kidney or colon. The spread of systemic cancer to the brain is a common complication for cancer patients. Eighty-one percent of people with central nervous system metastases are diagnosed after their primary cancer has been diagnosed and treated.

Brain metastases are commonly treated with surgical resection with curative intent if the patient has a good prognosis. If the patient is very ill, whole brain radiotherapy will be used. Whole brain radiotherapy normally extends survival to six months. There are no commonly used cytotoxic therapies for brain metastases because many physicians believe they are not effective in this indication.
Given the number of cases, the question arises how many of these cases are appropriate for Gamma Knife® surgery. “Appropriate” is defined as the patient stands a reasonable chance of obtaining a benefit in terms of control of brain disease and retention/improvement in quality of life with treatment with Leksell Gamma Knife®. To determine this, an analysis of RTOG protocol 79-16, a radiation therapy protocol on brain metastasis, was done in order to identify a group of patients who might benefit from more aggressive treatment such as Gamma Knife® surgery. The study identified four factors predictive of improved survival, and indicated likely benefit from a more aggressive treatment. The four factors are:

1. Karnofsky Performance Status (KPS) 70%
2. Absent or controlled primary disease
3. Age < 60
4. Evidence of metastasis to brain only

Patients with all four favorable factors had a 52% chance of surviving 200 days or longer while patients with three favorable factors had a 33% chance when treated using whole brain radiotherapy. This report recommended patients with three or more favorable factors be included in a more aggressive treatment protocol. The percentage of patients (in this study of 780 patients with brain metastases) with three or four factors totaled 47% of the patients. Combining this with the previously determined number of cases (170,000) yields a patient population of 79,900. It can be argued that this is an overly conservative prediction, in that
many patients with less than three of the four criteria above might still benefit from Gamma Knife® surgery as compared to other treatment techniques.

Using the 47% estimation, the United States population should generate 79,900 patients per year with brain metastases who would reasonably be expected to have benefit from Gamma Knife® surgery for their metastatic disease. Given a U.S. population of 290,000,000, this yields 275 patients per year per million inhabitants.

**Whole brain radiation combined with Gamma Knife® surgery**

Should fractionated radiotherapy be added to radiosurgery? The rationales for WBRT following surgical removal of a tumor cannot directly be implemented to the situation following Gamma Knife® surgery.

Recent reports indicate that overall survival may not be affected by the addition of whole brain radiotherapy after Leksell Gamma Knife® treatment of brain metastases. When treatment is successful and regional intracranial control of lesions is achieved, most patients die of progressive systemic disease.

Long-term survival after whole brain radiotherapy may carry a significant risk of dementia. DeAngelis et al report that 11% of patients who survived greater than one year after surgery and whole brain radiotherapy for brain metastases developed severe radiation-induced dementia.²

**Summary of Clinical Results**

Brain metastases are excellent targets for Gamma Knife® surgery, and the treatment has perhaps had its greatest role in the management of patients with metastatic brain tumors. Studies from across the
Today there are more than 283 papers discussing Gamma Knife Surgery for brain metastases. World have shown effectiveness in treatment of brain metastases. Local control provided by radiosurgery for the management of tumors in any brain location exceeds 85% on average.

As a minimally invasive procedure that provides excellent local control, palliation of symptoms, and avoids open craniotomy, radiosurgery is an attractive concept for both patients and physicians managing these problems.

Gamma Knife surgery is useful in recurrent disease treatment after whole brain radiotherapy as well as an adjunctive or definitive therapy of newly diagnosed disease with one or a few initial lesions. Unlike conventional radiotherapy, the response to Gamma Knife surgery appears to be as good for so-called “radioresistant” tumors (such as renal cell carcinoma and melanoma) as it is for radiosensitive tumors.

The first report of Leksell Gamma Knife treatment dates back to 1989 in Neurosurgery 1989, 25, 802-804. Today there are more than 190 papers discussing Gamma Knife surgery for brain metastases. There were 70 papers reporting over 6,926 patients in various studies between 1999 and December 2003. This has now become the largest single pathology being published for Gamma Knife surgery.

The University of Pittsburgh Medical Center has recently published a number of papers reviewing their results from brain metastases treatments;

There were 99 papers reporting over 13,900 patients in various studies 2001–2006


“Stereotactic radiosurgery for treatment of renal cell carcinoma metastases to the brain provides effective local tumor control in approximately 96% of patients and a median length of survival of 15 months.”

2. In another paper in International Journal of Radiation Oncology Biology Physics (INT-J RADIAT-ONCOL-BIOL-PHYS), 01 OCT 2003, Vol/Iss/Pg. 57/2 (452-464), they analyzed outcomes in patients who had survived at least one year after radiosurgery in 137 patients who were followed for a median of 18 months.


“Brain metastases were controlled well with radiosurgery alone as initial therapy. We advocate that WBRT should not be part of the initial treatment protocol for selected patients with one or two tumors with good control of their primary cancer, better Karnofsky Performance Scale score, and younger age, all of which are predictors of longer survival.”

Dade. Journal of neurosurgery, 2002 Dec, VOL: 97 (6), P: 1276-81. This is a retrospective review of 273 patients who had undergone Gamma Knife® surgery to treat a total of 627 non-small cell lung carcinoma metastases and they conclude: “Gamma Knife® surgery for NSCLC metastases affords effective local tumor control in approximately 84% of patients. Early detection of brain metastases, aggressive treatment of systemic disease, and a therapeutic strategy including GKS can afford patients an extended survival time.”

To highlight some other recent data from the University of Southern California and the University Hospital in Verona, Italy:


The largest single pathology being published for Gamma Knife® Surgery is brain metastases

458 consecutive patients with metastatic brain disease underwent Gamma Knife® surgery. The histological diagnosis was melanoma in 231 (50%), lung cancer in 94 (20.5%), breast cancer in 38 (8.3%), renal cell carcinoma (RCC) in 29 (6.3%), colon carcinoma in 13 (2.8%). Whole-brain radiotherapy (WBRT) either prior to or following Gamma Knife® surgery was performed in 114 patients (25%). The number of brain metastases (one-five), WBRT (yes vs. no), and age were not significant.
“Gamma Knife® radiosurgery provided an excellent palliation with low incidence of toxicity.”

2. Gamma Knife® radiosurgery for brain metastases: a primary therapeutic option., GerosaMassimo, Nicolato-Antonio, Foroni-Roberto, Zanotti-Bruno, Tomazzoli-Laura, Miscusi-Massimo, Alessandrini-Franco, Bricolo-Albino, Journal of neurosurgery, 2002 Dec, VOL: 97 (5 Suppl), P: 515-24. Treatment of 804 patients with brain metastases was evaluated and the local tumor control rate was 93%, with a mean follow-up period of 14 months. In the overall series, systemic disease progression was the main limiting factor with regard to patient life expectancy.

Utilization
More than 35,000 patients had been treated in the U.S. by June 2005 and more than 120,000 patients worldwide. This represents the largest single patient category for Gamma Knife® surgery. In the U.S., over 5,000 patients were treated between 2004 and June 2005.

Accumulated Number of Patients Treated, U.S.
Gamma Knife® surgery for the treatment of brain metastases is documented in hundreds of published articles encompassing studies ranging in size from less than ten patients to over four hundred patients. The following abstracts contain some of the more comprehensive studies conducted on the use of Gamma Knife® surgery to treat brain metastases and were instrumental in providing the evidence needed to gain market clearance for the treatment of brain metastases with the Leksell Gamma Knife.

**Brain Metastases – Multiple Metastasis**


**Title: Stereotactic radiosurgery for four or more intracranial metastases**

The purpose of this paper was to evaluate the outcomes after a single stereotactic radiosurgery procedure for the care of patients with 4 or more intracranial metastases. Two hundred five patients with primary malignancies underwent gamma knife radiosurgery for 4 or more intracranial metastases at one time. The 1-year local control rate was 71%, and the median time to progressive/new brain metastases was 9 months. Using the Radiation Therapy Oncology Group recursive partitioning analysis (RPA) classification system, the median overall survivals for RPA classes I, II, and III were 18, 9, and 3 months, respectively (p < 0.00001). **CONCLUSION:** Radiosurgery seems to provide survival benefit for patients with 4 or more intracranial metastases. Because total treatment volume was the most significant predictor of survival, the total volume of brain metastases, rather than the number of metastases, should be considered in identifying appropriate radiosurgery candidates.

**Brain Metastases – WBRT Role In Radiosurgical Management**

*Varlotto, John M. Et.al.* *IJROBP*, 62, 4, 1125-32, 2005

**Title: The impact of whole-brain radiation therapy on the long-term control and morbidity of patients surviving more than one year after gamma knife radiosurgery for brain metastases**

To better analyze how whole-brain radiotherapy (WBXRT) affects long-term tumor control and toxicity from the initial stereotactic radiosurgery (SRS) for brain metastases, we studied these outcomes in patients who had survived at least 1 year from SRS. We evaluated the results of gamma knife radiosurgery
for 160 brain metastases in 110 patients who were followed for a median of 18 months (range, 12-122 months) after SRS. At 1, 3, and 5 years, local tumor control was 84.1% +/- 5.5%, 68.6% +/- 8.7%, and 68.6% +/- 8.7% with SRS alone compared with 93.1% +/- 2.4%, 87.7% +/- 4.9%, and 65.7% +/- 10.2%.

with concurrent WBXRT and SRS (p = 0.0228, univariate). We found that WBXRT improved local control in patient subsets tumor volume >/=2 cc, peripheral dose </=16 Gy, single metastases, nonradioresistant tumors, and lung cancer metastases (p = 0.0069, 0.0080, 0.0083, 0.0184, and 0.0348). We found a trend for improved distal intracranial control with WBXRT for only nonradioresistant tumors (p = 0.0069, 0.0080, 0.0083, 0.0184, and 0.0348). WBXRT did not improve survival in the entire series (p = 0.5027) or in any subsets.

Title: Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial

Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases was evaluated in a randomized controlled trial of 132 patients with 1 to 4 brain metastases, each less than 3 cm in diameter. Patients were randomly assigned to receive WBRT plus SRS (65 patients) or SRS alone (67 patients). The median survival time and the 1-year actuarial survival rate were 7.5 months and 38.5% (95% confidence interval, 26.7%-50.3%) in the WBRT + SRS group and 8.0 months and 28.4% (95% confidence interval, 17.6%-39.2%) for SRS alone (P = .42).

CONCLUSIONS: Compared with SRS alone, the use of WBRT plus SRS did not improve survival for patients with 1 to 4 brain metastases, but intracranial relapse occurred considerably more frequently in those who did not receive WBRT. Consequently, salvage treatment is frequently required when up-front WBRT is not used.

Title: Radiosurgery with or without whole-brain radiotherapy for brain metastases: The patients' perspective regarding complications

To assess the patients’ perspective regarding current therapeutic options, we retrospectively surveyed 200 consecutive patients who underwent radiosurgery...
with or without WBRT. WBRT was used in 69% (72 of 104); all patients had radiosurgery. After WBRT, the following were noted: hair loss (88%; total regrowth in 24%), excess fatigue (95%), problems with short-term memory (72%), long-term memory (33%), concentration (61%), and depression (54%). Sixty-three percent of patients who had WBRT thought they had side effects after treatment compared with 34% who had radiosurgery only (P <0.001). Only 5% of RS patients reported fatigue. Side effects are most pronounced in those who received WBRT. Radiosurgery had fewer reported side effects and was believed by more patients or families to be effective.

Andrews, David W.; et.al. Lancet, 363, 9422, 1665-72, 2004
Title: Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial

Patients with one to three newly diagnosed brain metastases were randomly allocated either whole brain radiation therapy (WBRT) or WBRT followed by stereotactic radiosurgery boost. From January, 1996, to June, 2001, we enrolled 333 patients from 55 participating RTOG institutions. Univariate analysis showed that there was a survival advantage in the WBRT and stereotactic radiosurgery group for patients with a single brain metastasis (median survival time 6.5 vs 4.9 months, p=0.0393). Patients in the stereotactic surgery group were more likely to have a stable or improved Karnofsky Performance Status (KPS) score at 6 months’ follow-up than were patients allocated WBRT alone (43% vs 27%, respectively; p=0.03). WBRT and stereotactic boost treatment improved functional autonomy (KPS) for all patients and survival for patients with a single unresectable brain metastasis. WBRT and stereotactic radiosurgery should, therefore, be standard treatment for patients with a single unresectable brain metastasis and considered for patients with two or three brain metastases.

Brain Metastases – Lung and Breast Cancer

Gerosa, Massimo; et.al. Journal of neurosurgery, 102, 75-80, 2005
Title: Analysis of long-term outcomes and prognostic factors in patients with non-small cell lung cancer brain metastases treated by gamma knife radiosurgery

The authors conducted a study to evaluate the long-term outcomes and prognostic factors for survival in a large series of patients treated by gamma knife surgery (GKS) for non-small cell lung cancer (NSCLC) brain metastases.
The study is based on the retrospective analysis of clinical and radiological records obtained during a 10-year period (1993-2003), concerning 836 lesions in 504 patients. Analysis of long-term outcomes seemed to confirm that GKS is a primary therapeutic option in these patients. The 1-year local tumor control rate was 94%. The overall median survival was 14.5 months, with extremely rewarding quality of life indices.

Pan, Hung Chuan; et.al. Journal of neurosurgery, 102, 128-33, 2005
Title: Gamma knife surgery for brain metastases from lung cancer
The authors conducted a study to evaluate the safety and efficacy of gamma knife surgery (GKS) for the treatment of brain metastases from lung cancer. Between February 1993 and May 2003 191 patients underwent treatment for 424 brain metastases from non-small (171 cases) and small cell lung carcinoma (20 cases). There was no difference in median survival following combined whole-brain radiation therapy (WBRT) and gamma knife surgery (14 months) and GKS alone (15 months). CONCLUSIONS: There was no difference in response rates of the two tumor types, and WBRT did not improve the duration of survival.

Muacevic, Alexander. Et.al. Cancer, 100, 8, 1705-11, 2004
Title: Stereotactic radiosurgery for multiple brain metastases from breast carcinoma
During an 8-year period, 151 patients with a combined total of 620 brain metastases from breast carcinoma underwent 197 outpatient SRS procedures. The overall median survival duration was 10 months after SRS. Ninety-four percent of patients did not experience local brain tumor recurrence after radiosurgery. In addition, 70.2% of patients did not have disease recurrence in the brain. Most patients died of systemically progressing malignancy. Patients with RPA I, II, and III survived 34.9, 9.1, and 7.9 months, respectively. CONCLUSIONS: The results of the current study indicate that SRS is a feasible treatment concept for selected patients with multiple brain metastases from breast carcinoma.

Brain Metastases – Melanoma and Renal Cancer

Mingione, V.; et.al. Journal of Neurosurgery, 96, 3, 544-551, 2002
Title: Gamma surgery for melanoma metastases in the brain
The aim of this study was to evaluate the usefulness and limitations of gamma surgery (GS) in the treatment of brain metastases from melanoma. Imaging and clinical outcomes in 45 patients treated for 92 brain metastases from melanoma between October 1989 and October 1999 were retrospectively analyzed.
Twenty-four percent of the lesions disappeared, 35% shrank, 23% remained unchanged, and 18% increased in size. No undue radiation-induced changes were observed in the surrounding brain. Clinical data were available in all patients. No deaths or neurological morbidity related to GS was observed. The median survival time, calculated using the Kaplan-Meier method, was 10.4 months from the time of GS. CONCLUSIONS: Gamma surgery is effective in treating melanoma metastases in the brain. It appears that the radiobiology of a single high dose overcomes the radioresistance barrier, yielding better results than fractionated radiation.

Muacevic, A.; et.al. Minimally invasive neurosurgery, 47, 4, 203-8, 2004
Title: Stereotactic radiosurgery without radiation therapy providing high local tumor control of multiple brain metastases from renal cell carcinoma
The aim of this study was to analyse treatment effects after stereotactic radiosurgery (SRS) without whole brain radiation therapy (WBRT) as primary treatment for patients harboring brain metastases of renal cell carcinoma (RCC). During an 8-year period, 85 patients with 376 brain metastases from RCC underwent 134 outpatient SRS procedures. Overall median survival was 11.1 months after SRS. The local tumor control rate after SRS was 94 %. Most patients (78 %) died because of systemically progressing cancer. Patients of the RTOG groups I, II and III survived for 24.2 months, 9.2 months and 7.5 months, respectively. There was no permanent morbidity after SRS. Stereotactic radiosurgery alone achieves excellent local tumor control rates for patients with small brain metastases from renal cell carcinoma.¹

Gamma Knife® surgery – Published Papers, 1990–2006

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