Anatomical Location

Safety and efficacy of Gamma Knife surgery for brain metastases in eloquent locations.
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OBJECT: Brain metastases are the most frequently occurring cerebral tumors. Tumors that are located in eloquent cerebral parenchyma can cause considerable morbidity and may pose a significant challenge during surgery. Gamma Knife surgery (GKS) is a recognized treatment modality for brain metastases. This study was undertaken to assess the safety and efficacy of GKS, specifically for brain metastases in eloquent locations.

METHODS: Charts of patients harboring brain metastases that were treated by GKS at the Centre Hospitalier Universitaire de Sherbrooke between August 2004 and April 2008 were reviewed. Planning images were assessed by an independent neurosurgeon to assess tumor location. Eloquent locations included the primary motor, somatosensory, speech, and visual cortices; the basal ganglia; the thalamus; and the brainstem. Data on survival, tumor response, and complications were analyzed and compared with data published on surgical treatment of these lesions.

RESULTS: During the study period, 650 metastases in 295 patients were treated with GKS; of these, 164 metastases in 95 patients were located in eloquent areas. In this subgroup, the median age of patients was 59 years and women constituted 57.9% of the population. The median Karnofsky Performance Scale score was 80% (range 50%-100%). Patients were categorized according to their recursive partitioning analysis class: Class 1, 22.1%; Class 2, 70.5%; and Class 3, 7.4% of patients. Non-small cell lung cancer was the most common primary tumor (63.2% of metastases), followed by small cell lung (8.4%), breast (7.4%), colorectal (5.3%), and renal cell (4.2%) cancers, as well as melanoma (4.2%). The median dose to the tumor margin was 18 Gy (range 14-24 Gy). The median duration of survival after GKS was 8.2 months. The recursive partitioning analysis class was the most significant variable affecting survival (p < 0.0001). Immediate control was achieved in 92.9% of tumors, and 68.6% of tumors were still controlled at the last follow-up. The median time to tumor progression was 16 months. Higher margin dose (p = 0.002), the absence of edema (p = 0.009), and the non-small cell lung cancer tissue type (p = 0.035) positively affected response rates. Steroid medications were no longer used in 46% of patients after GKS. New neurological deficits occurred in 5.7% of patients and seizures in 5.7%. All these deficits were transient and patients completely recovered in response to a temporary course of steroids. Imaging studies showed that new edema occurred in 8.6% of treated metastases and biopsy-proven radiation necrosis in 1.4%.

CONCLUSIONS: Gamma Knife surgery is safe and effective for brain metastases located in eloquent areas.

Neurological complications and symptom resolution following Gamma Knife surgery for brain metastases 2 cm or smaller in relation to eloquent cortices.
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J Neurosurg. 2010 Dec;113 Suppl:53-64.
OBJECT: Reports on resection of tumors in or near eloquent cortices have noted neurological complications in up to 30% of patients. This paper contains an analysis of symptom resolution and neurological morbidity following 20-Gy Gamma Knife surgery (GKS) for supratentorial brain metastases < or = 2 cm in greatest diameter.

METHODS: The authors performed a retrospective analysis of 98 consecutively treated adults (33 men and 65 women with a median age of 61.4 years at the time of GKS) with Karnofsky Performance Scale score > or = 60, who underwent GKS for supratentorial brain metastases < or = 2 cm in diameter. Lesion location was classified as noneloquent (Grade I), near eloquent (Grade II), or eloquent (Grade III), in accordance with the grading system developed by the group at M. D. Anderson Cancer Center. Following treatment, the patients underwent MR imaging and clinical examinations at 6 weeks and every 3 months thereafter.

RESULTS: Ninety-eight patients underwent 20-Gy GKS for 131 metastases at initial presentation and 31 patients underwent salvage 20-Gy GKS for 76 new lesions, for a total of 207 lesions (mean lesion volume 0.44 cm3). Lesions were classified as follows: Grade I, 96 (46.4%); Grade II, 51 (24.6%); and Grade III, 60 (29%). Fifteen patients (2 with Grade II and 13 with Grade III lesions) presented with deficits referable to their lesions, yielding pre-GKS deficit rates of 7.2% per lesion and 15.3% per patient. The pre-GKS deficits improved or resolved in 10 patients (66.7%) at a median time of 2.8 months and remained stable in 3 patients (20%). Two patients (13.3%) experienced worsened neurological deficits. One patient who was neurologically intact prior to treatment developed a new hemiparesis (1 of 83 patients [1.2%]). The rates of permanent neurological deterioration following GKS for Grades I, II, and III lesions were 0% (0 of 96 tumors), 2% (1 of 51), and 3.3% (2 of 60), respectively. The pre-GKS neurological deficits and larger lesions were the most significant risk factors for post-GKS neurological deterioration.

CONCLUSIONS: Gamma Knife surgery performed using a 20-Gy dose provides amelioration of neurological deficits from brain metastases that are < or = 2 cm in diameter and located in or near eloquent cortices in nearly two-thirds of patients with a low incidence of morbidity. Consistent with the surgical literature, higher rates of neurological complications were observed as proximity to eloquent regions and lesion size increased. There was no neurological deterioration in patients harboring metastases in noneloquent areas.

Brain Stem

Stereotactic radiosurgery for single brainstem metastases: the Cleveland Clinic experience

PURPOSE: To assess the imaging and clinical outcomes of patients with single brainstem metastases treated with stereotactic radiosurgery (SRS).

MATERIALS AND METHODS: We retrospectively reviewed the data from patients with single brainstem metastases treated with SRS. Locoregional control and survival were calculated using the Kaplan-Meier method. Prognostic factors were assessed using a Cox proportional hazards model.

RESULTS: Between 1997 and 2007, 43 patients with single brainstem metastases were treated with SRS. The median age at treatment was 59 years, the median Karnofsky performance status was 80, and the median follow-up was 5.3 months. The median dose was 15 Gy (range, 9.6-24), and the median conformity and heterogeneity index was 1.7 and 1.9, respectively. The median survival was 5.8 months from the procedure date. Of the 33 patient with post-treatment imaging available, a complete radiographic response was achieved in 2 (4.7%), a partial response in 8 (18.6%), and stable disease in 23 (53.5%). The 1-year actuarial rate of local control, distant brain control, and overall survival was 85%, 38.3%, and 31.5%, respectively. Of the 43 patients, 8 (19%) died within 2 months of undergoing SRS, and 15 (36%) died within 3 months. On multivariate analysis, greater performance status (hazard ratio [HR], 0.95, p = .004), score index for radiosurgery (HR, 0.7; p = .004), graded prognostic assessment score (HR, 0.48; p = .003), and smaller tumor volume (HR, 1.23, p = .002) were associated with improved survival. No Grade 3 or 4 toxicities were observed.

CONCLUSION: The results of our study have shown that SRS is a safe and effective local therapy for patients with brainstem metastases.
Choroid Plexus

Stereotactic radiosurgical treatment of brain metastases to the choroid plexus.

PURPOSE: Choroid plexus metastases (CPM) are uncommon lesions. Consequently, optimal management of CPM is uncertain. We summarize our experience with stereotactic radiosurgery (SRS) of CPM.

METHODS AND MATERIALS: Sixteen consecutive patients with presumed CPM treated with SRS between 1997 and 2007 were examined. Twelve were men with a median age at diagnosis of CPM of 61.9 ± 9.9 years; 14 had metastases from renal cell carcinoma (RCC). All patients had controlled primary disease at the time of treatment for CPM. Four patients with RCC and 1 with non-small-cell lung cancer had undergone whole-brain radiotherapy (WBRT) previously and 2 had received SRS to other brain metastases. The disease-free interval from the primary diagnosis to CPM diagnosis averaged 39.3 ± 46.2 months (range, 1.0-156.3). Five patients were asymptomatic; of the remaining 11, none had symptoms related to CPM. All presented with a single CPM.

RESULTS: Average maximum diameter of the CPMs was 2.0 ± 1.0 cm (range, 0.9-4.1 cm); mean volume was 2.4 ± 2.6 cm^3 (range, 0.2-9.3). Median SRS dose was 24 Gy to the 53% isodose line (range, 14-24 Gy). Survival after SRS to the CPM was 25.3 ± 23.4 months (range, 3.2-101.6). Patients in Recursive Partitioning Analysis (RPA) class I (n = 10) had improved survival compared to those in class II (n = 6), as did those with better GPA scores. There were no local failures. After SRS, 1 patient underwent WBRT, 3 patients had one, and another had two subsequent SRS treatments to other brain lesions. Of the 14 patients who have died, 11 succumbed to systemic disease progression, 2 to progressive, multifocal central nervous system disease, and 1 to systemic disease with concurrent, stable central nervous system disease. There were no complications related to SRS.

CONCLUSIONS: Most CPMs are associated with RCC. SRS represents a safe and viable treatment option as primary modality for these metastases, with excellent outcomes.
Histology

Breast Cancer

Stereotactic radiosurgery as primary and salvage treatment for brain metastases from breast cancer.
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Journal of Neurosurgery, published online October 1, 2010; DOI: 10.3171/2010.8.JNS10461

OBJECT. To evaluate the role of stereotactic radiosurgery (SRS) in the management of brain metastases from breast cancer, the authors assessed clinical outcomes and prognostic factors for survival.

METHODS. The records from 350 consecutive female patients who underwent SRS for 1535 brain metastases from breast cancer were reviewed. The median patient age was 54 years (range 19–84 years), and the median number of tumors per patient was 2 (range 1–18 lesions). One hundred seventeen patients (33%) had a single metastasis to the brain, and 233 patients (67%) had multiple brain metastases. The median tumor volume was 0.7 cm³ (range 0.01–48.9 cm³), and the median total tumor volume for each patient was 4.9 cm³ (range 0.09–74.1 cm³).

RESULTS. Overall survival after SRS was 69%, 49%, and 26% at 6, 12, and 24 months, respectively, with a median survival of 11.2 months. Factors associated with a longer survival included controlled extracranial disease, a lower recursive partitioning analysis (RPA) class, a higher Karnofsky Performance Scale score, a smaller number of brain metastases, a smaller total tumor volume per patient, the presence of deep cerebral or brainstem metastases, and HER2/neu overexpression. Sustained local tumor control was achieved in 90% of the patients. Factors associated with longer progression-free survival included a better RPA class, fewer brain metastases, a smaller total tumor volume per patient, and a higher tumor margin dose. Symptomatic adverse radiation effects occurred in 6% of patients. Overall, the condition of 82% of patients improved or remained neurologically stable.

CONCLUSIONS. Stereotactic radiosurgery was safe and effective in patients with brain metastases from breast cancer and should be considered for initial treatment.

Gamma Knife surgery for metastatic brain tumors from primary breast cancer: treatment indication based on number of tumors and breast cancer phenotype.
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OBJECT: The goal of this study was to analyze prognostic factors for local tumor control and survival and indications for initial treatment with the Gamma Knife in patients with up to 10 metastatic brain tumors from primary breast cancer.

METHODS: Outcomes were retrospectively reviewed in 101 women with a total of 600 tumors, who underwent Gamma Knife surgery (GKS) for metastatic brain tumors between April 1992 and December 2008 at 1 institution. The inclusion criteria were up to 10 brain metastases, maximum diameter of tumor < 3 cm, and total tumor volume < 15 cm³. The exclusion criteria were poor systemic condition, presence of carcinomatous meningitis, and previous whole brain radiation treatment and/or craniotomy.

RESULTS: The mean tumor volume at GKS was 3.7 cm³ (range 0.016-14.3 cm³). The mean margin dose was 19 Gy (range 8-30 Gy). Neuroimaging showed that the local tumor growth control rate was 97%, and the tumor response rate was 82.3%. Larger tumor volume (p = 0.001) and lower margin dose (p = 0.001) were significant adverse prognostic factors for local tumor growth control according to a multivariate analysis. The number of brain metastatic lesions was 4 or fewer in 76 patients and 5 or more in 25 patients. The median overall survival time was 13 months. Multivariate analysis revealed that the presence of extracranial metastases (p = 0.041) and lesions that were not the human epidermal growth factor receptor-2 (HER2)-positive type (p = 0.001) were significant adverse prognostic factors for overall survival. The number of brain metastases was not statistically significant, except for a single metastasis. The median new lesion-free survival time after initial GKS was 9 months. Five or more lesions at initial GKS (p = 0.007) and younger patient age (p = 0.008) reduced survival significantly. The prevention of neurological death after GKS was 93.9% at 1 year, and a lower Karnofsky Performance Scale score (p = 0.009) was the only unfavorable factor. Median overall survival associated with the HER2-positive phenotype was significantly longer than survival associated with the other phenotypes (luminal
and triple-negative). There were no statistically significant differences between the 3 breast cancer phenotypes for the incidence of new brain metastases after initial GKS.

**CONCLUSIONS:** Initial GKS resulted in excellent local tumor control rates, which were associated with prolonged survival and a low risk of neurological death for patients with up to 10 metastatic brain tumors from primary breast cancer. The authors recommend periodic clinical and neuroradiological follow-up examinations after GKS in patients with 5 or more lesions at initial GKS, because they carry a high risk of development of new brain metastases, and in patients with the HER2-positive phenotype, because they tend to have a favorable prognosis in overall survival. Last, the authors recommend additional GKS or whole-brain radiation treatment for salvage treatment if new brain metastases occur.

**Treatment of cerebral metastases from breast cancer with stereotactic radiosurgery.**
Strahlenther Onkol 180[9]:590-596.

**BACKGROUND AND PURPOSE:** The role of stereotactic radiosurgery (SRS) alone or in combination with whole brain radiotherapy (WBRT) in the treatment of cerebral metastases from breast carcinoma is discussed controversially. To elucidate the role of SRS in this context, a retrospective study evaluating the benefit of SRS and prognostic factors for survival was performed.

**PATIENTS AND METHODS:** From 1986 to 2003, 62 patients with cerebral metastases from breast cancer were treated for 103 lesions. Ten patients received SRS alone (group 1), 13 patients were treated with WBRT and SRS as a focal boost (group 2), and 39 patients received WBRT and salvage SRS (group 3) for recurrent metastases at a later time point.

**RESULTS:** Survival was increased in patients receiving SRS only compared to WBRT and SRS as a focal boost. Patients < 40 years of age had a favorable outcome (p > 0.04). However, no other prognostic factors could be identified. Overall tolerance of radiation was acceptable. Median local control intervals were 9 months for all patients, 6.5 months in group 1, 4 months in group 2, and 9 months in group 3, respectively. There were no significant intergroup differences.

**CONCLUSION:** SRS alone is an effective treatment for patients with one to three brain metastases from breast cancer. A randomized trial should be performed to evaluate whether WBRT is a necessary component in the primary treatment of these patients. Salvage SRS is an effective therapy option after WBRT.

**Colorectal Cancer**

**Multidisciplinary treatment of brain metastases derived from colorectal cancer incorporating stereotactic radiosurgery: analysis of 78 patients.**
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**BACKGROUND:** We investigated the role of radiotherapy, including whole brain radiotherapy and stereotactic radiosurgery (SRS), and prognostic factors in patients with colorectal cancer (CRC) who developed brain metastases.

**PATIENTS AND METHODS:** The data of 78 patients who received multidisciplinary treatment from 1996 to 2007 were reviewed. Overall survival (OS), intracerebral control (ICC), and local control (LC) were retrospectively analyzed. Six potential prognostic factors were evaluated: age, gender, number of brain metastases, extracerebral metastases, recursive partitioning analysis (RPA) class, and interval from primary CRC diagnosis to radiotherapy.

**RESULTS:** The median OS and ICC for the entire cohort were 8 and 6 months, respectively. Surgical resection-incorporating treatment resulted in significant improvement in OS (P = .036). On multivariate analysis, OS and ICC were significantly correlated with lack of extracerebral metastases (P = .024 and P = .041, respectively), lower number of lesions (P < .001 and P = .007, respectively) and interval from primary CRC diagnosis (P < .001 and .005, respectively) whereas RPA class I-II demonstrated significance only for OS (P = .045). SRS-incorporating therapy revealed a 1-year LC probability of 85%. No association between LC and any of the potential prognostic factors was observed.

**CONCLUSION:** Our data indicate that surgery can prolong survival in CRC patients with brain metastases. SRS-incorporating treatment provides excellent LC rates and should be considered for patients with 1-3 lesions.
The strong association between survival and the prognostic factors identified in this study highlights a patient subset that may potentially benefit from new, more aggressive therapies.

**Gamma Knife surgery for brain metastases from colorectal cancer. Clinical article.**
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**OBJECT:** The outcomes after Gamma Knife surgery (GKS) were retrospectively analyzed in patients with brain metastases from radioresistant primary colorectal cancer to evaluate the efficacy of GKS and the prognostic factors for local tumor control and overall survival.

**METHODS:** The authors reviewed the medical records of 152 patients with 616 tumors. The group included 102 men and 50 women aged 35-85 years (mean age 64.4 years), who underwent GKS for metastatic brain tumors from colorectal cancer between April 1992 and September 2008 at Yokohama Rosai Hospital.

**RESULTS:** The mean prescription dose to the tumor margin was 18.5 Gy (range 0-30 Gy). The mean tumor volume at GKS was 2.0 cm³ (range 0.004-10.0 cm³). The primary tumors were located in the colon in 88 patients and the rectum in 64. The median interval between the diagnosis of primary lesions and the diagnosis of brain metastases was 27 months (range 0-180 months). The local tumor growth control rate, based on MR imaging, was 91.2%. The significant factors for unfavorable local tumor growth control, based on multivariate analysis, were larger tumor volume (p = 0.001) and lower margin dose (p = 0.016). The median overall survival time was 6 months. Lower Karnofsky Performance Scale (KPS) score (p = 0.026) and the presence of extracranial metastases (p = 0.004) at first GKS were significantly correlated with poor overall survival period in multivariate analysis. The cause of death was systemic disease in 112 patients and neurological disease in 13 patients. Leptomeningeal carcinomatosis was significantly correlated with a shorter duration of neurological survival in multivariate analysis (p < 0.0001).

**CONCLUSIONS:** Gamma Knife surgery is effective for suppression of local tumor growth in patients with brain metastases from radioresistant colorectal primary cancer. Therefore, clinical and radiological screening of intracranial metastases for patients with lower KPS scores and/or the presence of extracranial metastases as well as follow-up examinations after GKS for brain metastases should be performed periodically in patients with colorectal cancer, because the neurological prognosis is improved by initial and repeat GKS for newly diagnosed or recurrent tumors leading to a prolonged high-quality survival period.

**Gastric Cancer**

**The efficacy of gamma knife radiosurgery for advanced gastric cancer with brain metastases.**
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The aim of this study was to retrospectively investigate the efficacy of gamma knife radiosurgery for brain metastases from advanced gastric cancer (AGC) comparing whole brain radiotherapy (WBRT). Between January 1991 and May 2008, 56 patients with brain metastases from AGC, treated with GKR or WBRT, were reviewed to assess prognostic factors affecting survival. Most brain metastases were diagnosed based on MRI, both metachronous and synchronous brain metastases, adenocarcinoma and signet ring carcinoma were included, but excluded cases of gastric lymphoma. Fifteen patients with a median age of 54.0 years (range, 42-67 years) were treated with GKR: 11 were treated with GKR only, 2 with surgery plus GKR, 1 with repeated GKR, 1 with GKR plus WBRT, and the other 1 with WBRT plus GKR. Forty-one were treated with WBRT only. The median number of metastatic brain lesions was 3 (range, 1-15), and treatment involved 17.0 Gy (range 14-23.6 Gy), or 30 Gy with fractionated radiotherapy. The median survival after brain metastases for GKR treatment was 40.0 weeks [95% confidence interval (CI) 44.9-132.1 weeks] and WBRT was 9.0 weeks [95% CI, 8.8-21.9 weeks). The progression free survival of 15 GKR treated patients was 56.5 weeks [95% CI 33.4-79.5 weeks]. The recursive partitioning analysis (RPA) (class 2 vs. class 3) and use of GKR were correlated with prolonged survival in univariate and multivariate analyses. Age, sex, pathology, leptomeningeal seeding, tumor size (≥23 cm), extracranial metastases, single
metastasis, chemotherapy, and synchronous metastases were not correlated with a good prognosis in both univariate and multivariate analysis. Based on our study, the use of GKR and RPA class 2 resulted in more favorable clinical outcomes in patients with brain metastases from AGC.


Lung Cancer

**Gamma knife stereotactic radiosurgery for the management of incidentally-identified brain metastasis from non-small cell lung cancer.**

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Initial staging workup of non-small cell lung cancer (NSCLC) patients has led to increased identification of incidental brain metastases in patients who otherwise have minimal or no neurologic symptoms. We present our experience treating these metastases with stereotactic radiosurgery (SRS) alone and compare outcomes to those of patients with brain metastases treated with other strategies. We queried our neuro-oncology and radiation oncology databases for patients with incidentally-identified NSCLC brain metastases treated with upfront SRS alone between 1997 and 2006. We performed a retrospective analysis to evaluate outcomes in these patients. We found 26 patients with incidentally-identified NSCLC brain metastases (KPS 90-100) treated with SRS alone within 60 days of diagnosis of the metastases. These patients underwent SRS at a median 15 days from diagnosis to an average of 1.6 lesions (range: 1-7), with a mean lesion volume of 1.86 cm(3). The median prescription was 24 Gy delivered to the median 53% isodose line. The median survival for these patients was 8.2 months (mean 12.3 months) from diagnosis of brain metastases. Local CNS progression occurred in 2 patients (7.7%, mean 229.7 days). Survival was not statistically different from similar patients treated with whole brain radiotherapy (WBRT) (P = 0.98), WBRT + Surgery (P = 0.07) or WBRT + SRS (P = 0.62). Patients with incidentally-identified NSCLC brain metastases treated with SRS alone may achieve a survival rate comparable to patients managed with other standard therapeutic modalities. Our findings suggest that SRS alone may be a viable therapeutic option for patients with incidentally-discovered NSCLC brain metastases.

**Gamma Knife Radiosurgery for Treatment of Cerebral Metastases from Non-Small-Cell Lung Cancer.**

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Int J Radiat Oncol Biol Phys. 2011 Apr 27. [Epub ahead of print]

**PURPOSE:** To evaluate clinical and physico-dosimetric variables affecting clinical outcome of patients treated with Gamma Knife radiosurgery (GKRS) for brain metastases from non-small cell lung cancer (NSCLC).

**METHODS AND MATERIALS:** Between 2001 and 2006, 373 patients (298 men and 75 women, median age 65 years) with brain metastases from NSCLC underwent GKRS. All of them had KPS ≥ 60%, eight or fewer brain metastases, confirmed histopathological diagnosis and recent work-up (<3 months). Thirty-five patients belonged to recursive partitioning analysis (RPA) Class I, 307 patients were in RPA Class II, 7 patients were in RPA Class III. Median tumor volume was 3.6 cm(3). Median marginal dose was 22.5 Gy at 50% isodose; median 10 Gy and 12 Gy isodose volumes were 30.8 cm(3) and 15.8 cm(3), respectively. Follow-up with MRI was performed every 3 months. Overall survival data were collected from internal database, telephone interviews, and identifying registries.

**RESULTS:** Mean follow-up after GKRS was 51 months (range, 6 to 96 months); mean overall survival was 14.2 months. Of 373 patients, 29 were alive at time of writing, 104 had died of cerebral progression, and 176 had died of systemic progression. In 64 cases it was not possible to ascertain the cause. Univariate and multivariate analysis were adjusted for the following: RPA class, surgery, WBRT, age, gender, number of lesions, median tumor volume, median peripheral dose, and 10 Gy and 12 Gy volumes. Identified RPA class and overall tumor volume >5 cc were the only two covariates independently predictive of overall survival in patients who died of cerebral progression.

**CONCLUSIONS:** Global volume of brain disease should be the main parameter to consider for performing GKRS, which is a first-line therapy for patient in good general condition and controlled systemic disease.
**Gamma knife radiosurgery for brain metastasis of nonsmall cell lung cancer: is there a difference in outcome between morning and afternoon treatment?**


**BACKGROUND:** Circadian cell-cycle progression causes fluctuating radiosensitivity in many tissues, which could affect clinical outcomes. The purpose of this study was to determine whether outcomes of single-session gamma knife radiosurgery (GKRS) for metastatic nonsmall cell lung cancer (NSCLC) differ based on treatment time.

**METHODS:** Fifty-eight patients received GKRS between 10:00 am and 12:30 pm and 39 patients received GKRS between 12:30 pm and 3:00 pm. The mean peripheral dose was 18.6 Gy. The mean tumor size was 7.3 cm³.

**RESULTS:** Demographic and disease characteristics of the 2 groups were similar. Local control at 3 months was achieved in 97% (35/36) of patients who underwent GKRS early in the day versus 67% (8/12) of patients who underwent GKRS later in the day (chi-square, P = .014). Early GKRS was associated with better survival (median 9.5 months) than late GKRS (median 5 months) (Kaplan-Meier log-rank test, P = .025). Factors contributing to better survival in a Cox regression model included early treatment time (P = .004) and recursive partition analysis class (P < .001). Cause of death in the early treatment group was CNS-related in 6% (3/47) of patients versus 24% (8/34) of patients in the late treatment group (chi-square test, P = .026).

**CONCLUSIONS:** GKRS for metastatic NSCLC had better local control, better survival, and a lower rate of CNS-related cause of death when given earlier in the day versus later in the day. These retrospective data should encourage future study in brain radiosurgery and non-CNS stereotactic body radiotherapy series.

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**Early detection of metachronous brain metastases by biannual brain MRI follow-up may provide patients with non-small cell lung cancer with more opportunities to have radiosurgery.**


**PURPOSE:** Those who have brain metastases smaller than 30 mm in diameter and less than 5 in number can be treated less invasively with radiosurgery. This retrospective study evaluated the optimal brain magnetic resonance image (MRI) follow-up interval for non-small cell lung cancer (NSCLC) patients to detect radiosurgically manageable metachronous brain metastases (MBM).

**PATIENTS AND METHODS:** The records of 551 patients with primary NSCLC, treated in our institute between 2002 and 2007, were reviewed. The initial brain MRI was performed within one month after diagnosis of NSCLC, and the follow-up brain MRI interval was at the discretion of physicians. The interval between the last MRI in which brain metastases were not found and the first MRI in which brain metastases were found was defined as the critical MRI interval (CMI). The relationship between CMI and the maximum size or number of MBM was evaluated.

**RESULTS:** Among reviewed patients, the initial MRI of 38 patients showed brain metastases and 29 patients were diagnosed as MBM. In these MBM patients, the median interval from diagnosis of NSCLC to diagnosis of brain metastases was 8.9 months. The median CMI was 4.7 (range: 1.6-18.9) months. All brain metastases smaller than 30 mm in maximum diameter were found when CMI was shorter than 6.0 months, although 5 or more brain metastases in number were detected even by shorter CMI than 3 months.

**CONCLUSION:** Early detection of MBM by biannual MRI follow-up may provide NSCLC patients with more opportunities to have less invasive treatment.

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**Two cases of lung cancer patients with postoperative brain metastases obtaining long-term survival after gamma knife radiosurgery.**

[Article in Japanese]

We report two cases of lung cancer patients with postoperative solitary brain metastases obtaining long-term survival after gamma knife stereotactic radiosurgery. Both were seventies men and had good performance status without active extracranial disease. In one case, an asymptomatic metastatic brain tumor 1.8 cm in maximum diameter appeared one year and two months after the operation and was irradiated with gamma knife resulting in complete local control for seven years. He is alive with solitary lung metastasis in good performance status. In the other case, gamma knife was employed for a metastatic brain tumor 2.7 cm in maximum diameter that appeared nine months after the operation accompanying incomplete left hemiplegia. Six months later, the tumor was enlarged and gamma knife was repeated, but the tumor growth could not be suppressed. Following deterioration of hemiplegia and appearance of convulsion, he died of neurological disorder three years and two months after the onset of brain metastasis. Gamma knife stereotactic radiosurgery for metastatic brain tumors is less invasive and a repeatable technique, and is expected to provide a good local control and a survival benefit for appropriately selected patients.

**Radiosurgery for brain metastases from primary lung carcinoma.**

**PURPOSE:** Brain metastases are a common problem in patients with lung cancer. This retrospective review was performed to describe the efficacy and toxicity of stereotactic radiosurgery for brain metastases from lung carcinoma and to evaluate prognostic factors for survival.

**PATIENTS AND METHODS:** A retrospective review was performed of 113 patients with the diagnosis of lung carcinoma who underwent radiosurgery with or without whole-brain radiotherapy for management of newly diagnosed or recurrent, single, or multiple brain metastases from 1991 through 1998 at the University of California, San Francisco. Freedom from progression and survival were measured from the date of radiosurgery and estimated using the Kaplan-Meier method. Prognostic factors were evaluated with the log-rank test and Cox proportional hazards models.

**RESULTS:** The median patient age at the time of radiosurgery was 59 years (range, 37-82 years), and the median Karnofsky performance score was 90 (range, 50-100). The median survival time from radiosurgery was 12.0 months overall, 13.9 months for 41 patients treated with radiosurgery alone initially, 14.5 months for 19 patients treated with radiosurgery and whole-brain radiotherapy initially, and 10.0 months for 53 patients with recurrent brain metastases. Among newly diagnosed patients, multivariate analysis showed that improved survival was associated with absence of extracranial metastases and fewer brain metastases. Among patients with recurrent brain metastases, improved survival was associated with higher Karnofsky performance score, control of the primary tumor, and fewer metastases. Measured by lesion, 1-year local freedom from progression probabilities were 81% for radiosurgery alone, 86% for radiosurgery and whole-brain radiotherapy, and 65% for radiosurgery performed after recurrence. In patients with newly diagnosed brain metastases, there was a significantly greater risk of developing subsequent brain metastases and of worse overall brain freedom from progression after radiosurgery alone versus radiosurgery and whole-brain radiotherapy. One-year brain freedom from progression probabilities were 13% without salvage therapy and 62% with salvage therapy in the 41 patients treated initially with radiosurgery alone, versus 67% without salvage therapy and 89% with salvage therapy in the 19 patients treated initially with radiosurgery plus whole-brain radiotherapy.

**DISCUSSION:** Radiosurgery is an effective therapy for selected patients with newly diagnosed or recurrent brain metastases from lung carcinoma. Initial whole-brain radiotherapy with radiosurgery appears to improve brain control but not survival. Prospective, randomized trials are needed to further investigate the role of radiosurgery with and without whole-brain radiotherapy for brain metastases.

**Three irradiation treatment options including radiosurgery for brain metastases from primary lung cancer.**

**PURPOSE:** To determine local control and survival rates in 92 patients with 145 brain metastases treated with three options of radiotherapy including stereotactic radiosurgery (SR).

**METHODS:** Between July 1994 and August 2002, 92 consecutive patients with 145 metastases were treated with a SR, 34 with initially SR alone, 22 initially with an association of whole-brain radiotherapy (WBRT) and 36 with SR alone for recurrent new brain metastasis after WBRT. At time of treatment, extracranial disease was controlled in 46 (50%) and uncontrolled in 46 (50%). Pathologies were adenocarcinoma in 54 cases (59%), squamous cell
carcinoma in 14 cases (15%), small cell carcinoma in 10 cases (11%) and miscellaneous in 14 cases (15%). All patients underwent only one treatment fraction for 1 or 2 metastases in 73 cases (83%) and for more than 2 metastases for the others.

**RESULTS:** The characteristics of patients and metastases in the group treated initially with SR alone and in the group treated initially with WBRT+SR were comparable. Median follow-up was 29 months (18-36). Overall, the median and the 1- and 2-year rates of overall survival were, respectively, 9 months, 37 and 20%. A controlled extracranial disease, a high Karnofsky index and a low number of metastasis were independent prognostic factor of overall survival, respectively, HR 0.53 (95% CI 0.31-0.90, P=0.01), HR 0.95 (95% CI 0.92-0.97, P=0.0002), and HR 0.48 (95% CI 0.25-0.90, P=0.02). Thirteen metastases were not controlled (9%). Six-month and 1-year local control rate were, respectively, 93 and 86%. High delivered dose was an independent prognostic factor of local control, HR 0.41 (95% CI 0.18-0.95, P=0.03). A controlled extracranial disease was favourable independent prognostic factor of brain free-disease free survival, HR 0.47 (95% CI 0.2-0.98, P=0.04). Although there was a trend of a better local control, overall and brain disease free survivals rates in the WBRT+SR group compared to SR alone one, the difference were not statistically different.

**CONCLUSION:** Local control and survival rates are acceptable for a palliative treatment for the three option of treatment. In this series, the number of patients is not enough great to conclude to the necessity of the association of WBRT to SR. Re-irradiation is a safe treatment after new metastases appeared in previously irradiated area.

### Melanoma

**Gamma knife surgery in brain melanomas: absence of extracranial metastases and tumor volume strongest indicators of prolonged survival.**

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**OBJECTIVE:** To review a series of patients who underwent Gamma Knife surgery (GKS) to identify prognostic factors for local growth control and survival.

**METHODS:** During the period 1996-2006, 77 patients (42 men and 35 women) with a total of 143 metastases underwent GKS. A solitary lesion was present in 40 patients (51.9%).

**RESULTS:** Growth control was achieved in 114 of 128 (89.1%) tumors and 59 of 70 (84.3%) patients. The median survival was 7 months (range 0-73 months) after GKS and 67 months (range 4-327 months) from the time of diagnosis. Patients with absence of extracranial disease lived longer than patients with more widespread disease-median 16 months (range 3-52 months) versus 6 months (range 0-73 months; P = 0.014). A total tumor volume of less than 5 cc was associated with longer survival (P = 0.041). Survival was significantly longer in recursive partitioning analysis (RPA) class 1 (22 months) than RPA class 2 (7 months) and RPA class 3 (3 months; P = 0.008). Even in cases of treatment failure with tumor growth or appearance of new metastases, GKS slowed down the cerebral disease with no significant reduction in the duration of survival.

**CONCLUSIONS:** GKS for melanoma brain metastasis provides a high rate of local tumor control. Survival is longest for well-functioning patients with absence of extracranial metastases or with an intracerebral total tumor volume less than 5 cc.

**Outcome predictors of Gamma Knife surgery for melanoma brain metastases.**


**OBJECT.** To evaluate the role of stereotactic radiosurgery (SRS) in the management of brain metastases from melanoma, the authors assessed clinical outcomes and prognostic factors for survival and tumor control.

**METHODS.** The authors reviewed 333 consecutive patients with melanoma who underwent SRS for 1570 brain metastases from cutaneous and mucosal/acral melanoma. The patient population consisted of 109 female and 224 male patients with a median age of 53 years. Two hundred eleven patients (63%) had multiple metastases. One hundred eighteen patients (35%) underwent whole-brain radiation therapy (WBRT). The target volume ranged from 0.1 cm(3) to 37.2 cm(3). The median marginal dose was 18 Gy.

**RESULTS.** Actuarial survival rates were 70% at 3 months, 47% at 6 months, 25% at 12 months, and 10% at 24 months after radiosurgery. Factors associated with longer survival included controlled extracranial disease, better
Karnofsky Performance Scale score, fewer brain metastases, no prior WBRT, no prior chemotherapy, administration of immunotherapy, and no intratumoral hemorrhage before radiosurgery. The median survival for patients with a solitary brain metastasis, controlled extracranial disease, and administration of immunotherapy after radiosurgery was 22 months. Sustained local tumor control was achieved in 73% of the patients. Sixty-four (25%) of 259 patients who had follow-up imaging after SRS had evidence of delayed intratumoral hemorrhage. Sixteen patients underwent a craniotomy due to intratumoral hemorrhage. Seventeen patients (6%) had asymptomatic and 21 patients (7%) had symptomatic radiation effects. Patients with ≤ 8 brain metastases, no prior WBRT, and the recursive partitioning analysis Class I had extended survivals (median 54.3 months).

**CONCLUSIONS.** Stereotactic radiosurgery is an especially valuable option for patients with controlled systemic disease even if they have multiple metastatic brain tumors.

**Ovarian Cancer**

**Gamma-knife radiosurgery as an optimal treatment modality for brain metastases from epithelial ovarian cancer.**


**OBJECTIVES:** The objectives of this study are to analyze the clinical feature and overall survival rate of patients with brain metastases from epithelial ovarian cancer (EOC) and to compare the treatment outcomes of gamma-knife radiosurgery (GKS) and whole-brain radiation therapy (WBRT).

**METHODS:** A retrospective chart review of patients diagnosed with brain metastases from EOC in a single institution between 1983 and 2005 was performed. Of 1413 patients with EOC, 18 (1.3%) developed brain metastases. Fifteen patients who were treated with GKS or WBRT were enrolled for this study. Seven patients were treated with GKS, and the remaining patients were treated with WBRT as a primary treatment modality.

**RESULTS:** The median age at the time of diagnosis of the primary cancer and brain metastases was 55 and 56 years, respectively. The median interval between the diagnosis of the primary cancer and brain metastases was 28 months. It was significantly associated with the overall survival rate after the diagnosis of ovarian cancer (p=0.017). There were 5 patients (33.3%) with extracranial metastases. Five patients (33.3%) had a solitary brain lesion. The median survival time after the diagnosis of brain metastases was 14 months (range, 1-59 months). Patients who were treated with GKS after brain metastasis had a longer survival time (median, 29 months) than those treated with WBRT (median, 6 months) (p=0.0061).

**CONCLUSION:** For the control of brain metastases, GKS seems to be an effective modality. GKS improves the overall survival of the patients with brain metastases from EOC.

**Renal Cell Carcinoma**

**Outcome Predictors of Gamma Knife Radiosurgery for Renal Cell Carcinoma Metastases.**


**CONFLICT OF INTEREST NOTIFICATION:** Drs. Lunsford and Kondziolka are consultants with AB Elekta. Dr. Lunsford is a stockholder in AB Elekta.

**BACKGROUND:** Although whole brain radiation therapy (WBRT) has been a standard palliative management for brain metastases from renal cell carcinoma, its benefit has been elusive because of radiobiological resistance.

**OBJECTIVE:** We evaluated the role of stereotactic radiosurgery (SRS) in the management of brain metastases from renal cell carcinoma.

**METHODS:** We reviewed records from 158 consecutive patients (male=111, female=47) who underwent SRS for 531 brain metastases from renal cell carcinoma. The median patient age was 61 years (38-83 years) and the median number of tumors per patient was one (1-10). Seventy-nine patients (50%) had solitary brain metastasis. Fifty-seven patients (36%) underwent prior WBRT. The median total tumor volume for each patient was 3.0 cc (0.09-47 cc).
RESULTS: The overall survival after SRS was 60%, 38%, and 19% at 6, 12, and 24 months, respectively, with a median survival of 8.2 months. Factors associated with longer survival included younger age, longer interval between primary diagnosis and brain metastases, lower Recursive Partitioning Analysis (RPA) class, higher Karnofsky Performance status (KPS), smaller number of brain metastases, and no prior WBRT. Median survival for patients with < 2 brain metastases, higher KPS (> 90), and no prior WBRT was 12 months after SRS. Sustained local tumor control was achieved in 92% of patients. Symptomatic adverse radiation effects occurred in 7%. Overall, 70% of patients improved or remained neurologically stable.

CONCLUSION: SRS is an especially valuable option for patients with higher KPS and smaller number of brain metastases from renal cell carcinoma.

Early Significant Tumor Volume Reduction After Radiosurgery in Brain Metastases from Renal Cell Carcinoma Results in Long-Term Survival.
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PURPOSE: To retrospectively evaluate survival of patients with brain metastasis from renal cell carcinoma (RCC) after radiosurgery.

PATIENTS AND METHODS: Between 1998 and 2010, 46 patients were treated with radiosurgery, and the total number of lesions was 99. The mean age was 58.9 years (range, 33-78 years). Twenty-six patients (56.5%) had a single brain metastasis. The mean tumor volume was 3.0 cm\(^3\) (range, 0.01-35.1 cm\(^3\)), and the mean marginal dose prescribed was 20.8 Gy (range, 12-25 Gy) at the 50% isodose line. A patient was classified into the good-response group when the sum of the volume of the brain metastases decreased to less than 75% of the original volume at a 1-month follow-up evaluation using MRI.

RESULTS: As of December 28, 2010, 39 patients (84.8%) had died, and 7 (15.2%) survived. The overall median survival time was 10.0 ± 0.4 months (95% confidence interval, 9.1-10.8). After treatment, local tumor control was achieved in 72 (84.7%) of the 85 tumors assessed using MRI after radiosurgery. The good-response group survived significantly longer than the poor-response group (median survival times of 18.0 and 9.0 months, respectively; \(p = 0.025\)). In a multivariate analysis, classification in the good-response group was the only independent prognostic factor for longer survival (\(p = 0.037\); hazard ratio = 0.447; 95% confidence interval, 0.209-0.953).

CONCLUSIONS: Radiosurgery seems to be an effective treatment modality for patients with brain metastases from RCC. The early significant tumor volume reduction observed after radiosurgery seems to result in long-term survival in RCC patients with brain metastases.

Stereotactic radiosurgery as single-modality treatment of incidentally identified renal cell carcinoma brain metastases.

BACKGROUND: Initial staging evaluation of patients with renal cell carcinoma (RCC) has led increasingly to the diagnosis of brain metastases in patients who are otherwise neurologically asymptomatic. We present our experience treating patients with incidentally identified brain metastases with initial stereotactic radiosurgery (SRS) monotherapy and compare outcomes with those of patients treated at our institution with other strategies and with those reported in the literature.

METHODS: We conducted a retrospective outcomes analysis in patients with incidentally identified RCC brain metastasis treated with initial SRS monotherapy. Our radiation oncology and tumor databases were reviewed, identifying 80 patients treated between 1990 and 2006.

RESULTS: We found 19 patients with asymptomatic, incidentally identified brain metastasis (KPS,90-100) treated with SRS monotherapy within 60 days of diagnosis. Stereotactic radiosurgery was performed at a mean of 17.8 days from diagnosis to an average of 3.1 lesions (range, 3-11; mean lesion volume, 1.72 cm\(^3\); mean total volume, 4.53 cm\(^3\)). The mean prescription was 21.3 Gy delivered to the mean 59.97% isodose line. The mean survival for these patients was 21.5 months (median, 12.6 months) and was not statistically different from survival in similar patients treated with other therapeutic modalities. Local control was achieved in 95% of patients; distant central nervous system progression occurred in 79% of patients at a mean of 450 days.

CONCLUSIONS: We demonstrate that patients with incidentally identified RCC brain metastases treated with initial SRS monotherapy achieved a survival rate comparable with that of patients managed with standard
therapeutic modalities. Our findings suggest that SRS alone is an attractive therapeutic option for patients with incidentally identified brain metastases from RCC.
Comparison to Alternative Technologies

**Apparatus dependence of normal brain tissue dose in stereotactic radiosurgery for multiple brain metastases.**

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**OBJECT:** Technical improvements in commercially available radiosurgery platforms have made it practical to treat a large number of intracranial targets. The goal of this study was to investigate whether the dose to normal brain when planning radiosurgery to multiple targets is apparatus dependent.

**METHODS:** The authors selected a single case involving a patient with 12 metastatic lesions widely distributed throughout the brain as visualized on contrast-enhanced CT. Target volumes and critical normal structures were delineated with Leksell Gamma Knife Perfexion software. The imaging studies including the delineated contours were digitally exported into the CyberKnife and Novalis multileaf collimator-based planning systems for treatment planning using identical target dose goals and dose-volume constraints. Subsets of target combinations (3, 6, 9, or 12 targets) were planned separately to investigate the relationship of number of targets and radiosurgery platform to the dose to normal brain.

**RESULTS:** Despite similar target dose coverage and dose to normal structures, the dose to normal brain was strongly apparatus dependent. A nonlinear increase in dose to normal brain volumes with increasing number of targets was also noted.

**CONCLUSIONS:** The dose delivered to normal brain is strongly dependent on the radiosurgery platform. How general this conclusion is and whether apparatus-dependent differences are related to differences in hardware design or differences in dose-planning algorithms deserves further investigation.

Comparisons to Alternative Treatments

**Radiosurgery versus Surgical Resection**

**Single brain metastasis: Whole-brain irradiation plus either radiosurgery or neurosurgical resection.**

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**BACKGROUND:** The current study was conducted to compare neurosurgical resection (NR) followed by whole-brain irradiation (WBI) (NR + WBI) with WBI followed by radiosurgery (WBI + RS) in patients with a single brain metastasis.

**METHODS:** The outcome of 41 patients treated with WBI + RS was retrospectively compared with 111 patients who received NR + WBI with respect to local control of the treated metastasis and survival. Eleven additional potential prognostic factors were investigated, including WBI schedule, patient age, patient gender, Karnofsky performance score (KPS), primary tumor type, extracerebral metastases, recursive partitioning analysis (RPA) class, interval between the first diagnosis of cancer to the treatment of brain metastasis, metastatic site, maximum diameter of the metastasis, and graded prognostic assessment (GPA) score.

**RESULTS:** The 1-year local control rates were 87% after WBI + RS and 56% after NR + WBI (P = .001). Using the Cox proportional hazards model, the treatment regimen remained significant (risk ratio [RR], 2.46; 95% confidence interval [95% CI], 1.29-5.17 [P = .005]). On the multivariate analysis, local control was also found to be associated with the maximum diameter of the metastasis. The 1-year survival rates were 61% after WBI + RS and 53% after NR + WBI (P = .16). Acute and late toxicities were similar in both groups. On the multivariate analysis, KPS, extracerebral metastases, RPA class, and the GPA score were found to be independent predictors of survival.

**CONCLUSIONS:** The use of WBI + RS resulted in significantly better local control of the treated metastasis than NR + WBI. Survival was not found to be significantly different in either group. Because WBI + RS is less invasive than NR + WBI, it appears to be preferable for many patients with a single brain metastasis. These results should be confirmed in a randomized trial.
Microsurgery plus whole brain irradiation versus Gamma Knife surgery alone for treatment of single metastases to the brain: a randomized controlled multicentre phase III trial.

BACKGROUND: Is Gamma Knife surgery alone as effective as surgery plus whole brain irradiation (WBRT) for patients with a single, small-sized brain metastasis?

METHODS: Patients aged between 18 and 80 years harboring a single, resectable metastasis < or =3 cm in diameter, a Karnofsky performance score (KPS) > or =70, and a stable systemic disease were randomly assigned to microsurgery plus WBRT or Gamma Knife surgery alone. The primary end point was length of survival, secondary end points were recurrence of tumor in the brain, health related quality of life, and treatment related toxicity.

RESULTS: Due to poor patient accrual, the study was stopped prematurely. The final analysis was based on 33 patients in the surgery and 31 patients in the radiosurgery group. Treatment results did not differ in terms of survival (P = 0.8), neurological death rates (P = 0.3), and freedom from local recurrence (P = 0.06). Patients of the radiosurgery group experienced more often distant recurrences (P = 0.04); after adjustment for the effects of salvage radiosurgery this difference was lost (P = 0.4). Radiosurgery was associated with a shorter hospital stay, less frequent and shorter timed steroid application (P < or = 0.001), and lower frequency of grade 1/2 toxicities (according to the RTOG/EORTC CNS toxicity criteria, P < or = 0.01). Improved scores for role functioning and quality of life were seen 6 weeks after radiosurgery (P < 0.05); this difference was lost 6 months after treatment.

CONCLUSIONS: In patients harboring a single, small-sized metastasis, Gamma Knife surgery alone is less invasive; local tumor control seems to be as high as after surgery plus WBRT. Distant tumor control, however, is significantly less frequently achieved (after radiosurgery alone). The role of radiosurgical salvage therapy (alternatively to WBRT) for distant tumor control deserves further prospective evaluation.

PURPOSE: To determine whether neurosurgery (NS) or stereotactic radiosurgery (RS) provided better local tumor control and enhanced patient survival.

METHODS AND MATERIALS: Retrospective review of all solitary brain metastases (SBM) patients newly diagnosed at Mayo Clinic Rochester between 1991 and 1999. Eligible patients satisfied tumor size and SBM site criteria to qualify for both NS and RS.

RESULTS: There were no significant differences between 74 NS and 23 RS patients in terms of baseline characteristics (age, gender, systemic disease type, systemic disease status, signs/symptoms at SBM presentation) or percent of patients who received whole brain radiotherapy. Median follow-up for alive patients was 20 months (range 0-106 months). There was no significant difference in patient survival (p = 0.15); the 1-year survival rate was 56% for the RS patients and 62% for the NS patients. Multivariate Cox regression analysis found that a significant prognostic factor for survival was a performance score of 0 or 1. There was a significant (p = 0.020) difference in local tumor control between NS and RS for solitary brain metastasis; none of the RS group had local recurrence compared to 19 (58%) of the NS group.

CONCLUSION: The need for a Phase III study comparing these two techniques appears to be supported by the data from this study.

Defining the role of stereotactic radiosurgery versus microsurgery in the treatment of single brain metastases.

Stereotactic radiosurgery (RS) and surgery have proved to be effective treatment modalities for brain metastasis. We followed 133 patients whose treatment for intracranial disease was either RS or a single surgical resection at the University of Vienna from August 1992 through October 1996. All patients who received additional Whole Brain Radiotherapy were included. This was a retrospective, case-control study comparing these treatment modalities. Sixty-seven patients were treated by RS and 66 patients were treated by microsurgery. The median size of the treated lesions for RS patients was 7800 mm³, and 12500 mm³ for microsurgery patients, respectively. The median dose delivered to the tumour margin for RS patients was 17 gray. The median survival for patients after RS was 12 months, and 9 months for patients after microsurgery. This difference was not statistically significant (p = 0.19). Comparison of local tumour control, defined as absence of regrowth of a treated lesion, showed that tumours following RS had a preferred local control rate (p < 0.05). Univariate and multivariate analysis showed that this fact was due to a greater response rate of “radioresistant” metastasis to RS (p < 0.005). Postradiosurgical complications included the onset of peritumoural oedema (n = 5) and radiation necrosis (n = 1). Two patients after microsurgery experienced local wound infection. One postoperative death occurred due to pulmonary embolism in this group. On the basis of our data we conclude that RS and microsurgery combined with Whole Brain Radiotherapy are comparable modalities in treating single brain metastasis. Concerning morbidity and local tumour control, in particular in cases of "radioresistant" primary tumours, RS is superior. Therefore we advocate RS except for cases of large tumours (> 3 cm in maximum diameter) and for those with mass effect.

Surgery and radiotherapy compared with gamma knife radiosurgery in the treatment of solitary cerebral metastases of small diameter.

OBJECT: The aim of this retrospective study was to compare treatment results of surgery plus whole-brain radiation therapy (WBRT) with gamma knife radiosurgery alone as the primary treatment for solitary cerebral metastases suitable for radiosurgical treatment.

METHODS: Patients who had a single circumscribed tumor that was 3.5 cm or smaller in diameter were included. Treatment results were compared between microsurgery plus WBRT (52 patients, median tumor dose 50 Gy) and radiosurgery alone (56 patients, median prescribed tumor dose 22 Gy). In case of local/distant tumor recurrence in the radiosurgery group, additional radiosurgical treatment was administered in patients with stable systemic disease. Survival time was analyzed using the Kaplan-Meier method, and prognostic factors were obtained from the Cox model. The patient groups did not differ in terms of age, gender, pretreatment Karnofsky Performance Scale (KPS) score, duration of symptoms, tumor location, histological findings, status of the primary tumor, time to metastasis, and cause of death. Patients who suffered from larger lesions underwent surgery (p < 0.01). The 1-year survival rate (median survival) was 53% (68 weeks) in the surgical group and 43% (35 weeks) in the
radiosurgical group \((p = 0.19)\). The 1-year local tumor control rates after surgery and radiosurgery were 75% and 83%, respectively \((p = 0.49)\), and the 1-year neurological death rates in these groups were 37% and 39% \((p = 0.8)\). Shorter overall survival time in the radiosurgery group was related to higher systemic death rates. A pretreatment KPS score of less than 70 was a predictor of unfavorable survival. Perioperative morbidity and mortality rates were 7.7% and 1.6% in the resection group, and 8.9% and 1.2% in the radiosurgery group, respectively. Four patients presented with transient radiogenic complications after radiosurgery.

**CONCLUSIONS:** Radiosurgery alone can result in local tumor control rates as good as those for surgery plus WBRT in selected patients. Radiosurgery should not be routinely combined with radiotherapy.

**Stereotactic radiosurgery versus microsurgical resection for the initial treatment of metastatic cancer to the brain.**


The use of Stereotactic radiosurgery for the treatment of intracranial metastases from systemic cancer has grown considerably in the last few years. Review of the literature, however, reveals a paucity of well-controlled studies to substantiate this expansion. We conducted this study to address the issue of survival after treatment with either stereotactic radiosurgery or surgical resection. Whole brain radiation was instituted in both treatment arms. This was a retrospective, case-controlled study comparing patients whose only treatment for intracranial disease was either stereotactic radio-surgery or a single surgical resection. Controlling for age, histology, whole brain radiation, tumor size, number of intracranial lesions, and pre-procedural Karnofsky performance scores, we believe this study to be the most rigorous analysis to date. Patients in the radiosurgery group survived longer (median survival = 12.5 months) than those in the surgically resected group (median survival = 8 months). Statistical analysis of these curves did not show a significant difference. Considering only length of patient survival, there is no statistical difference between stereotactic radiosurgery and microsurgical resection for the treatment of new brain metastases from systemic cancer. This conclusion is based on strict criteria as outlined in the text. A larger, prospective, randomized investigation is needed to more definitively address the issue.

**Surgery versus radiosurgery in the treatment of brain metastasis.**


Surgery and radiosurgery are effective treatment modalities for brain metastasis. To compare the results of these treatment modalities, the authors followed 13 patients treated by radiosurgery and 62 patients treated by surgery who were retrospectively matched. Patients were matched according to the following criteria: histological characteristics of the primary tumor, extent of systemic disease, preoperative Karnofsky Performance Scale score, time to brain metastasis, number of brain metastases, and patient age and sex. For patients treated by radiosurgery, the median size of the treated lesion was 1.96 cm\(^3\) (range 0.41-8.25 cm\(^3\)) and the median dose was 20 Gy (range 12-22 Gy). The median survival was 7.5 months for patients treated by radiosurgery and 16.4 months for those treated by surgery; this difference was found to be statistically significant using both univariate \((p = 0.0018)\) and multivariate \((p = 0.0009)\) analyses. The difference in survival was due to a higher rate of mortality from brain metastasis in the radiosurgery group than in the surgery group \((p < 0.0001)\) and not due to a difference in the rate of death from systemic disease \((p = 0.28)\). Log-rank analysis showed that the higher mortality rate found in the radiosurgery group was due to a greater progression rate of the radiosurgically treated lesions \((p = 0.0001)\) and not due to the development of new brain metastasis \((p = 0.75)\). On the basis of their data, the authors conclude that surgery is superior to radiosurgery in the treatment of brain metastasis. Patients who undergo surgical treatment survive longer and have a better local control. The data lead the authors to suggest that the indications for radiosurgery should be limited to surgically inaccessible metastatic tumors or patients in poor medical condition. Surgery should remain the treatment of choice whenever possible.
Radiosurgery versus Whole Brain Radiation Therapy

A meta-analysis evaluating stereotactic radiosurgery, whole-brain radiotherapy, or both for patients presenting with a limited number of brain metastases.

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BACKGROUND: To perform a meta-analysis on newly diagnosed brain metastases patients treated with whole-brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS) boost versus WBRT alone, or in patients treated with SRS alone versus WBRT and SRS boost.

METHODS: The meta-analysis primary outcomes were overall survival (OS), local control (LC), and distant brain control (DBC). Secondary outcomes were neurocognition, quality of life (QOL), and toxicity. Using published Kaplan-Meier curves, results were pooled using hazard ratios (HR).

RESULTS: Two RCTs reported on WBRT and SRS boost versus WBRT alone. For multiple brain metastases (2-4 tumors) we conclude no difference in OS, and LC significantly favored WBRT plus SRS boost. Three RCTs reported on SRS alone versus WBRT plus SRS boost (1-4 tumors). There was no difference in OS despite both LC and DBC significantly favoring WBRT plus SRS boost. Although secondary endpoints could not be pooled for meta-analysis, those RCTs evaluating SRS alone conclude better neurocognition using the validated Hopkins Verbal Learning Test, no adverse risk in deteriorating Mini-Mental Status Exam scores or in maintaining performance status, and fewer late toxicities. We conclude insufficient data for QOL outcomes.

CONCLUSIONS: For selected patients, we conclude no OS benefit for WBRT plus SRS boost compared with SRS alone. Although additional WBRT improves DBC and LC, SRS alone should be considered a routine treatment option due to favorable neurocognitive outcomes, less risk of late side effects, and does not adversely affect the patients performance status. Cancer 2011. © 2011 American Cancer Society.

Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial.

Dr Eric L Chang MD, Jeffrey S Wefel PhD, Prof Kenneth R Hess PhD, Pamela K Allen PhD, Prof Frederick F Lang MD, David G Kornguth MD, Rebecca B Arbuckle MS, Prof J Michael Swint PhD, Prof Almon S Shiu PhD, Prof Moshe H Maor MD, Prof Christina A Meyers PhD (2009)
The Lancet Oncology, Volume 10, Issue 11, Pages 1037 - 1044, November 2009

BACKGROUND: It is unclear whether the benefit of adding whole-brain radiation therapy (WBRT) to stereotactic radiosurgery (SRS) for the control of brain-tumours outweighs the potential neurocognitive risks. We proposed that the learning and memory functions of patients who undergo SRS plus WBRT are worse than those of patients who undergo SRS alone. We did a randomised controlled trial to test our prediction.

METHODS: Patients with one to three newly diagnosed brain metastases were randomly assigned using a standard permuted block algorithm with random block sizes to SRS plus WBRT or SRS alone from Jan 2, 2001, to Sept 14, 2007. Patients were stratified by recursive partitioning analysis class, number of brain metastases, and radiosensitive histology. The randomisation sequence was masked until assignation, at which point both clinicians and patients were made aware of the treatment allocation. The primary endpoint was neurocognitive function: objectively measured as a significant deterioration (5-point drop compared with baseline) in Hopkins Verbal Learning Test—Revised (HVLT-R) total recall at 4 months. An independent data monitoring committee monitored the trial using Bayesian statistical methods. Analysis was by intention-to-treat. This trial is registered at www.ClinicalTrials.gov, number NCT00548756.

FINDINGS: After 58 patients were recruited (n=30 in the SRS alone group, n=28 in the SRS plus WBRT group), the trial was stopped by the data monitoring committee according to early stopping rules on the basis that there was a high probability (96%) that patients randomly assigned to receive SRS plus WBRT were significantly more likely to show a decline in learning and memory function (mean posterior probability of decline 52%) at 4 months than patients assigned to receive SRS alone (mean posterior probability of decline 24%). At 4 months there were four deaths (13%) in the group that received SRS alone, and eight deaths (29%) in the group that received SRS plus WBRT. 73% of patients in the SRS plus WBRT group were free from CNS recurrence at 1 year, compared with 27% of patients who received SRS alone (p=0.0003). In the SRS plus WBRT group, one case of grade 3 toxicity (seizures, motor neuropathy, depressed level of consciousness) was attributed to radiation treatment. In the group that received SRS, one case of grade 3 toxicity (aphasia) was attributed to radiation treatment. Two cases of grade 4 toxicity in the group that received SRS alone were diagnosed as radiation necrosis.
INTERPRETATION: Patients treated with SRS plus WBRT were at a greater risk of a significant decline in learning and memory function by 4 months compared with the group that received SRS alone. Initial treatment with a combination of SRS and close clinical monitoring is recommended as the preferred treatment strategy to better preserve learning and memory in patients with newly diagnosed brain metastases.

Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone.

PURPOSE: To determine how the omission of whole brain radiotherapy (WBRT) affects the neurocognitive function of patients with one to four brain metastases who have been treated with stereotactic radiosurgery (SRS).

METHODS AND MATERIALS: In a prospective randomized trial between WBRT+SRS and SRS alone for patients with one to four brain metastases, we assessed the neurocognitive function using the Mini-Mental State Examination (MMSE). Of the 132 enrolled patients, MMSE scores were available for 110.

RESULTS: In the baseline MMSE analyses, statistically significant differences were observed for total tumor volume, extent of tumor edema, age, and Karnofsky performance status. Of the 92 patients who underwent the follow-up MMSE, 39 had a baseline MMSE score of < or =27 (17 in the WBRT+SRS group and 22 in the SRS-alone group). Improvements of > or =3 points in the MMSES of 9 WBRT+SRS patients and 11 SRS-alone patients (p = 0.85) were observed. Of the 82 patients with a baseline MMSE score of > or =27 or whose baseline MMSE score was < or =26 but had improved to > or =27 after the initial brain treatment, the 12-, 24-, and 36-month actuarial free rate of the 3-point drop in the MMSE was 76.1%, 68.5%, and 14.7% in the WBRT+SRS group and 59.3%, 51.9%, and 51.9% in the SRS-alone group, respectively. The average duration until deterioration was 16.5 months in the WBRT+SRS group and 7.6 months in the SRS-alone group (p = 0.05).

CONCLUSION: The results of the present study have revealed that, for most brain metastatic patients, control of the brain tumor is the most important factor for stabilizing neurocognitive function. However, the long-term adverse effects of WBRT on neurocognitive function might not be negligible.

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OBJECT: Resection and whole-brain radiation therapy (WBRT) have classically been the standard treatment for a single metastasis to the brain. The objective of this study was to evaluate the use of Gamma Knife surgery (GKS) as an alternative to WBRT in patients who had undergone resection and to evaluate patient survival and local tumor control.

METHODS: The authors retrospectively reviewed the charts of 150 patients treated with a combination of stereotactic radiosurgery and resection of a cranial metastasis at their institution between April 1997 and September 2009. Patients who had multiple lesions or underwent both WBRT and GKS were excluded, as were patients for whom survival data beyond the initial treatment were not available. Clinical and imaging follow-up was assessed using notes from clinic visits and MR imaging studies when available. Follow-up data beyond the initial treatment and survival data were available for 68 patients.

RESULTS: The study included 37 women (54.4%) and 31 men (45.6%) (mean age 60 years, range 28-89 years). In 45 patients (66.2%) there was systemic control of the primary tumor when the cranial metastasis was identified. The median duration between resection and radiosurgery was 15.5 days. The median volume of the treated cavity was 10.35 cm(3) (range 0.9-45.4 cm(3)), and the median dose to the cavity margin was 15 Gy (range 14-30 Gy), delivered to the 50% isodose line (range 50%-76% isodose line). The patients' median preradiosurgery Karnofsky Performance Scale (KPS) score was 90 (range 40-100). During the follow-up period we identified 27 patients (39.7%) with recurrent tumor located either local or distant to the site of treatment. The median time from primary treatment of metastasis to recurrence was 10.6 months. The patients' median length of survival (interval between first treatment of cerebral metastasis and last follow-up) was 13.2 months. For the patient who died during follow-up, the median time from diagnosis of cerebral metastasis to death was 11.5 months. The median duration of survival from diagnosis of the primary cancer to last follow-up was 30.2 months. Patients with a pretreatment KPS score ≥ 90 had a median survival time of 23.2 months, and patients with a pretreatment KPS...
score < 90 had a median survival time of 10 months (p < 0.008). Systemic control of disease at the time of metastasis was not predictive of increased survival duration, although it did tend to improve survival.

**CONCLUSIONS:** Although the debate about the ideal form of radiation treatment after resection continues, these findings indicate that GKS combined with surgery offers comparable survival duration and local tumor control to WBRT for patients with a diagnosis of a single metastasis.

### Whole-brain radiotherapy versus stereotactic radiosurgery for patients in recursive partitioning analysis classes 1 and 2 with 1 to 3 brain metastases.


**BACKGROUND:** The authors investigated whether stereotactic radiosurgery (SRS) alone improved outcomes for patients in recursive partitioning analysis (RPA) Classes 1 and 2 who had 1 to 3 brain metastases compared with whole-brain radiotherapy (WBRT).

**METHODS:** Data regarding 186 patients in RPA Classes 1 and 2 who had 1 to 3 brain metastases and who received either 30 to 40 Gy of WBRT (n = 91 patients) or 18 to 25 Gy SRS (n = 95 patients) were analyzed retrospectively. Eight other potential prognostic factors were evaluated regarding overall survival (OS), entire brain control (BC), local control (LC) of treated metastases, and brain control distant from treated metastases (distant control [DC]): Those 8 factors were age, sex, performance status, tumor type, number of brain metastases, extracranial metastases, RPA class, and interval from tumor diagnosis to radiotherapy.

**RESULTS:** On multivariate analysis of OS, age (risk ratio [RR], 1.51; P = .024), Karnofsky performance status (KPS) (RR, 1.98; P = .002), and extracranial metastases (RR, 2.26; P < .001) were significant, whereas the radiation regimen was not significant (P = .89). On multivariate analysis of BC, only the radiation regimen (RR, 1.33; P = .003) was found to be significant. On multivariate analysis of LC, radiation regimen (RR, 1.63; P < .001) and sex (RR, 1.62; P = .022) were significant. On multivariate analysis of DC, KPS (RR, 1.85; P = .049) and extracranial metastases (RR, 1.69; P = .047) were significant. The radiation regimen was not found to be significant even on univariate analysis (P = .80). In RPA class subgroup analyses, BC and LC were better after SRS than WBRT for patients in RPA Classes 1 and 2, whereas OS and DC did not differ significantly.

**CONCLUSIONS:** For patients in RPA Classes 1 and 2 who had 1 to 3 brain metastases, SRS alone was associated with improved BC and LC compared with 30 to 40 Gy WBRT, whereas OS and DC were not significantly different. Similar results were observed in separate subgroup analyses of patients in RPA Class 1 and RPA Class 2.

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


**CONTEXT:** In patients with brain metastases, it is unclear whether adding up-front whole-brain radiation therapy (WBRT) to stereotactic radiosurgery (SRS) has beneficial effects on mortality or neurologic function compared with SRS alone.

**OBJECTIVE:** To determine if WBRT combined with SRS results in improvements in survival, brain tumor control, functional preservation rate, and frequency of neurologic death.

**DESIGN, SETTING, AND PATIENTS:** Randomized controlled trial of 132 patients with 1 to 4 brain metastases, each less than 3 cm in diameter, enrolled at 11 hospitals in Japan between October 1999 and December 2003.

**INTERVENTIONS:** Patients were randomly assigned to receive WBRT plus SRS (65 patients) or SRS alone (67 patients).

**MAIN OUTCOME MEASURES:** The primary end point was overall survival; secondary end points were brain tumor recurrence, salvage brain treatment, functional preservation, toxic effects of radiation, and cause of death.

**RESULTS:** 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). The 12-month brain tumor recurrence rate was 46.8% in the WBRT + SRS group and 76.4% for SRS alone group (P < .001). Salvage brain treatment was less frequently required in the WBRT + SRS group (n = 10) than with SRS alone (n = 29) (P < .001). Death was attributed to neurologic causes in 22.8% of patients in the WBRT + SRS group and in 19.3% of those treated with SRS alone (P = .64). There were no significant differences in systemic and neurologic functional preservation and toxic effects of radiation.

**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.
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.


PURPOSE: 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.

METHODS AND MATERIALS: 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. Eighty-two patients had a solitary brain metastasis and 28 patients had multiple metastases. Seventy patients (116 tumors) were treated with initial radiosurgery and WBXRT, whereas 40 patients (44 lesions) initially received radiosurgery alone. Median treatment volume was 1.9 cc in the entire group, 2.3 cc in the WBXRT group, and 1.6 cc in the SRS alone group. Median tumor dose was 16 Gy (range, 12-21 Gy).

RESULTS: 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 > or =2 cc, peripheral dose < or =16 Gy, single metastases, nonradioresistant tumors, and lung cancer metastases (p = 0.0069, 0.0080, 0.0184, and 0.0348). Distal intracranial failure developed at 1, 3, and 5 years in 26.0% +/- 7.1%, 74.5% +/- 9.4%, and 74.5% +/- 9.4% with SRS alone compared with 20.7% +/- 4.9%, 49.0% +/- 8.7%, and 61.8% +/- 12.8% with concurrent WBXRT and SRS (p = 0.0657). We found a trend for improved distal intracranial control with WBXRT for only nonradioresistant tumors (p = 0.054). Postradiosurgery complications developed in 2.8% +/- 1.2% and 10.7% +/- 3.5% at 1 and 3-5 years and was unaffected by WBXRT (p = 0.7721). WBXRT did not improve survival in the entire series (p = 0.5027) or in any subsets.

CONCLUSIONS: In this retrospective study of 1-year survivors of SRS for brain metastases, the addition of concurrent WBXRT to SRS was associated with an improved local control rate in patient subsets with tumor volume > or =2 cc, peripheral dose < or =16 Gy, single metastases, nonradioresistant tumors, and specifically lung cancer metastases. A trend was noted for improved distal intracranial control for patients having nonradioresistant tumors. Distant intracranial relapse >1 year posttreatment is a significant problem with or without initial WBXRT.

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.


BACKGROUND: Brain metastases occur in up to 40% of all patients with systemic cancer. We aimed to assess whether stereotactic radiosurgery provided any therapeutic benefit in a randomised multi-institutional trial directed by the Radiation Therapy Oncology Group (RTOG).

METHODS: 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. Patients were stratified by number of metastases and status of extracranial disease. Primary outcome was survival; secondary outcomes were tumour response and local rates, overall intracranial recurrence rates, cause of death, and performance measurements.

FINDINGS: From January, 1996, to June, 2001, we enrolled 333 patients from 55 participating RTOG institutions--167 were assigned WBRT and stereotactic radiosurgery and 164 were allocated WBRT alone. 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). By multivariate analysis, survival improved in patients with an RPA class 1 (p<0.0001) or a favourable histological status (p=0.0121).

INTERPRETATION: 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.
Survival in relation to radiotherapeutic modality for brain metastasis: whole brain irradiation vs. gamma knife radiosurgery.

The purpose of this report is to evaluate and compare the survival of patients with brain metastasis (BRM) treated by whole brain irradiation (WBI) using linear energy accelerator (LINAC) and by stereotactic radiosurgery using gamma knife. This study consists of a series of 67 patients with BRM treated with WBI between 1998 and 1999 and 53 patients with BRM treated with gamma knife radiosurgery (GKRS) between 2000 and 2001. A retrospective study of the data was performed and the overall survival between these 2 groups was analyzed. The comparability of these 2 groups was tested by chi2 and t test values. Log-rank test was used in the survival comparison. The 1-year survival rate was 26.3% and 22.6%, and corresponding mean survival was 7.8 months and 6.7 months for WBI and GKRS groups, respectively. There was no statistically significant difference between these 2 groups’ survival. It was evident from imaging defined lesions that with GKRS the lesions were reduced, stabilized, or disappeared in 89% of cases. Survival of patients with BRM treated with WBI or GKRS was similar in these series. The present study suggests that good tumor response by GKRS does not translate in longer patient survival.

A multi-institutional review of radiosurgery alone vs. radiosurgery with whole brain radiotherapy as the initial management of brain metastases.

PURPOSE: Data collected from 10 institutions were reviewed to compare survival probabilities of patients with newly diagnosed brain metastases managed initially with radiosurgery (RS) alone vs. RS + whole brain radiotherapy (WBRT).

METHODS AND MATERIALS: A database was created from raw data submitted from 10 institutions on patients treated with RS for brain metastases. The major exclusion criteria were resection of a brain metastasis and interval from the end of WBRT until RS >1 month (to try to ensure that the up-front intent was to combine RS + WBRT and that RS was not given for recurrent brain metastases). Survival was estimated using the Kaplan-Meier method from the date of first treatment for brain metastases until death or last follow-up. Survival times were compared for patients managed initially with RS alone vs. RS + WBRT using the Cox proportional hazards model to adjust for known prognostic factors or Radiation Therapy Oncology Group recursive partitioning analysis (RPA) class.

RESULTS: Out of 983 patients, 31 were excluded because treatment began after 6/1/98; 159 were excluded because brain metastases were resected; 179 were excluded because there was an interval >1 month from WBRT until RS; and 45 were excluded for other reasons. Of the 569 evaluable patients, 268 had RS alone initially (24% of whom ultimately had salvage WBRT), and 301 had RS + up-front WBRT. The median survival times for patients treated with RS alone initially vs. RS + WBRT were 14.0 vs. 15.2 months for RPA Class 1 patients, 8.2 vs. 7.0 months for Class 2, and 5.3 vs. 5.5 months for Class 3, respectively. With adjustment by RPA class, there was no survival difference comparing RS alone initially to RS + up-front WBRT (p = 0.33, hazard ratio = 1.09).

CONCLUSIONS: Omission of up-front WBRT does not seem to compromise length of survival in patients treated with RS for newly diagnosed brain metastases.

Gamma knife radiosurgery for brain metastases: do patients benefit from adjuvant external-beam radiotherapy? An 18-month comparative analysis.
Stereotact Funct Neurosurg 79[3-4]:262-271.

OBJECTIVE: To analyze 18 months of results of gamma knife stereotactic radiosurgery in the treatment of brain metastases and determine factors affecting outcome by examining the effectiveness of additional external-beam radiotherapy (XRT).

MATERIALS AND METHODS: Between January 2000 and September 2001, 61 patients with 103 tumors diagnosed as cerebral metastases were treated with gamma knife. Mean patient age was 57 years (range = 36-81). Lung carcinoma (55.7%) was the most common primary cancer, followed by melanoma (14.8%) and breast carcinoma (11.5%). Mean KPS of the patients was 70 (range = 50-90). Twenty-seven patients had solitary metastases while 34
had multiple tumors. Forty-three patients (59 tumors in total) received only radiosurgery, while 18 patients (44 tumors in total) had prior XRT. Tumor volume ranged from 0.5 to 33 cm$^3$ (mean = 9.74 cm$^3$). Mean marginal dose prescription to the tumor was 15 Gy (range = 11-21 Gy).

RESULTS: Median follow-up was 11 months. Twenty-one patients (34.4%) were alive at last follow-up and 40 (65.6%) had died. Seventeen deaths (42.5%) were reported to be due to progressive brain disease, while 23 deaths (57.5%) were due to uncontrolled primary. Control of the treated lesions was achieved in 45 patients (73.8%) and 84 tumors (81.6%). Mean overall survival of the patients is 8 months (range = 1-19 months). The actuarial 12-month tumor control rate using the Kaplan-Meier method for this series is 68.2 +/- 0.06%. Results of the log-rank test revealed that younger age (<55 years), small tumor volume (<10 cm$^3$), and increasing tumor dose (>15 Gy) correlated with improved brain disease-free survival (p < 0.05). Overall survival, local tumor control rate and the freedom from brain disease period (based on the appearance of new brain tumors after radiosurgery) were analyzed separately for the groups receiving radiosurgery alone and those with prior XRT to detect any additional benefit of XRT. No statistically significant difference was found between the two groups for any of the considered outcomes.

CONCLUSION: Gamma knife stereotactic radiosurgery is a safe and effective treatment option for patients with cerebral metastases. It provides survival benefits and improves quality of life by achieving excellent control of the brain disease, irrespective of patients’ age or number of brain tumors. The addition of XRT in younger patients with small brain metastases does not improve survival and/or control of the brain disease.

Radiosurgery for brain metastases: is whole brain radiotherapy necessary?

PURPOSE: Because whole brain radiotherapy (WBRT) may cause dementia in long-term survivors, selected patients with brain metastases may benefit from initial treatment with radiosurgery (RS) alone reserving WBRT for salvage as needed. We reviewed results of RS +/- WBRT in patients with newly diagnosed brain metastasis to provide background for a prospective trial.

METHODS AND MATERIALS: Patients with single or multiple brain metastases managed initially with RS alone vs. RS + WBRT (62 vs. 43 patients) from 1991 through February 1997 were retrospectively reviewed. The use of upfront WBRT depended on physician preference and referral patterns. Survival, freedom from progression (FFP) endpoints, and brain control allowing for successful salvage therapy were measured from the date of diagnosis of brain metastases. Actuarial curves were estimated using the Kaplan-Meier method. Analyses to adjust for known prognostic factors were performed using the Cox proportional hazards model (CPHM) stratified by primary site.

RESULTS: Survival and local FFP were the same for RS alone vs. RS + WBRT (median survival 11.3 vs. 11.1 months and 1-year local FFP by patient 71% vs. 79%, respectively). Brain FFP (scoring new metastases and/or local failure) was significantly worse for RS alone vs. RS + WBRT (28% vs. 69% at 1 year; CPHM adjusted p = 0.03 and hazard ratio = 0.476). However, brain control allowing for successful salvage of a first failure was not significantly different for RS alone vs. RS + WBRT (62% vs. 73% at 1 year; CPHM adjusted p = 0.56).

CONCLUSIONS: The omission of WBRT in the initial management of patients treated with RS for up to 4 brain metastases does not appear to compromise survival or intracranial control allowing for salvage therapy as indicated. A randomized trial of RS vs. RS + WBRT is needed to assess survival, quality of life, and cost in good-prognosis patients with newly diagnosed brain metastases.
increased for patients who received WBRT (15.4 vs 8.3 months; P=.08). Additionally, there was a suggestion that increased doses for patients treated with RS only resulted in improved outcome. Four lesions were suspicious for radiation necrosis by magnetic resonance imaging (MRI); in one of the four lesions, radiation necrosis was confirmed histologically. The incidence of transient low-grade toxicity was 18%; symptoms could be treated by the temporary administration of steroids.

CONCLUSION: RS is an effective, noninvasive means of controlling brain metastases when used alone or in combination with WBRT. There is a trend for superior local control and especially in patients without extracranial disease for superior survival when RS is used in conjunction with WBRT. Randomized trials would seem to be warranted, comparing the benefit of RS with or without additional WBRT.
Multiple Metastases

Gamma Knife surgery as sole treatment for multiple brain metastases: 2-center retrospective review of 1508 cases meeting the inclusion criteria of the JLGK0901 multi-institutional prospective study.

OBJECT: The authors retrospectively reviewed the results of Gamma Knife surgery (GKS) used as the sole treatment for brain metastases in patients who met the eligibility criteria for the ongoing JLGK0901 multi-institutional prospective trial. They also discuss the anticipated results of the JLGK0901 study.

METHODS: Data from 1508 consecutive cases were analyzed. All of the patients were treated at the Gamma Knife House of Chiba Cardiovascular Center or the Mito Gamma House of Katsuta Hospital between 1998 and 2007 and met the following JLGK0901 inclusion criteria: 1) newly diagnosed brain metastases, 2) 1-10 brain lesions, 3) less than 10 cm³ volume of the largest tumor, 4) no more than 15 cm³ total tumor volume, 5) no findings of CSF dissemination, and 6) no impairment of activities of daily living (Karnofsky Performance Scale score < 70) due to extracranial disease. At the initial treatment, all visible lesions were irradiated with GKS without upfront whole-brain radiation therapy. Thereafter, gadolinium-enhanced MR imaging was performed every 2-3 months, and new distant lesions were appropriately retreated with GKS. Patients were divided into groups according to numbers of tumors: Group A, single lesions (565 cases); Group B, 2-4 tumors (577 cases); and Group C, 5-10 tumors (366 cases). The differences in overall survival (OS) were compared between groups.

RESULTS: The median age of the patients was 66 years (range 19-96 years). There were 963 men and 545 women. The primary tumors were in the lung in 1114 patients, gastrointestinal tract in 179, breast in 105, urinary tract in 66, and other sites in 44. The overall mean survival time was 0.78 years (0.99 years for Group A, 0.68 years for Group B, and 0.62 years for Group C). The differences between Groups A and B (p < 0.0001) and between Groups B and C (p = 0.0312) were statistically significant. Multivariate analysis revealed significant prognostic factors for OS to be sex (poor prognostic factor: male, p < 0.0001), recursive partitioning analysis class (Class I vs Class II and Class II vs III, both p < 0.0001), primary site (lung vs breast, p = 0.0047), and number of tumors (Group A vs Group B, p < 0.0001). However, no statistically difference was detected between Groups B and C (p = 0.1027, hazard ratio 1.124, 95% CI 0.999-1.265).

CONCLUSIONS: The results of this retrospective analysis revealed an upper CI of 1.265 for the hazard ratio, which was lower than the 1.3 initially set by the JLGK0901 study. The JLGK0901 study is anticipated to show noninferiority of GKS as sole treatment for patients with 5-10 brain metastases compared with those with 2-4 in terms of OS.

Analysis of radiosurgical results in patients with brain metastases according to the number of brain lesions: is stereotactic radiosurgery effective for multiple brain metastases?

OBJECT: Whole-brain radiation therapy (WBRT), open resection, and stereotactic radiosurgery (SRS) are widely used for treatment of metastatic brain lesions, and many physicians recommend WBRT for multiple brain metastases. However, WBRT can be performed only once per patient, with rare exceptions. Some patients may require SRS for multiple metastatic brain lesions, particularly those patients harboring more than 10 lesions. In this paper, treatment results of SRS for brain metastasis were analyzed, and an attempt was made to determine whether SRS is effective, even in cases involving multiple metastatic brain lesions.

METHODS: The authors evaluated the cases of 323 patients who underwent SRS between October 2005 and October 2008 for the treatment of metastatic brain lesions. Treatment was performed using the Gamma Knife model C or Perfexion. The patients were divided into 4 groups according to the number of lesions visible on MR images: Group 1, 1-5 lesions; Group 2, 6-10 lesions: Group 3, 11-15 lesions; and Group 4, > 15 lesions. Patient survival and progression-free survival times, taking into account both local and distant tumor recurrences, were analyzed.

RESULTS: The patients consisted of 172 men and 151 women with a mean age at SRS of 59 years (range 30-89 years). The overall median survival time after SRS was 10 months (range 8.7-11.4 months). The median survival
time of each group was as follows: Group 1, 10 months; Group 2, 10 months; Group 3, 13 months; and Group 4, 8 months. There was no statistical difference between survival times after SRS (log-rank test, p = 0.554), although the probability of development of new lesions in the brain was greater in Group 4 (p = 0.014). Local tumor control rates were not statistically different among the groups (log-rank test, p = 0.989); however, remote disease progression was more frequent in Group 4 (log-rank test, p = 0.014).

CONCLUSIONS: In this study, patients harboring more than 15 metastatic brain lesions were found to have faster development of new lesions in the brain. This may be due to the biological properties of the patients' primary lesions, for example, having a greater tendency to disseminate hematogenously, especially to the brain, or a higher probability of missed or invisible lesions (microscopic metastases) to treat on stereotactic MR images at the time of radiosurgery. However, the mean survival times after SRS were not statistically different between groups. According to the aforementioned results, SRS may be a good treatment option for local control of metastatic lesions and for improved survival in patients with multiple metastatic brain lesions, even those patients who harbor more than 15 metastatic brain lesions, who, after SRS, may have early and easily detectable new metastatic lesions.

Radiosurgery alone for 5 or more brain metastases: expert opinion survey.
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OBJECT: Oligometastatic brain metastases may be treated with stereotactic radiosurgery (SRS) alone, but no consensus exists as to when SRS alone would be appropriate. A survey was conducted at 2 radiosurgery meetings to determine which factors SRS practitioners emphasize in recommending SRS alone, and what physician characteristics are associated with recommending SRS alone for ≥ 5 metastases.

METHODS: All physicians attending the 8th Biennial Congress and Exhibition of the International Stereotactic Radiosurgery Society in June 2007 and the 18th Annual Meeting of the Japanese Society of Stereotactic Radiosurgery in July 2009 were asked to complete a questionnaire ranking 14 clinical factors on a 5-point Likert-type scale (ranging from 1 = not important to 5 = very important) to determine how much each factor might influence a decision to recommend SRS alone for brain metastases. Results were condensed into a single dichotomous outcome variable of “influential” (4-5) versus “not influential” (1-3). Respondents were also asked to complete the statement: “In general, a reasonable number of brain metastases treatable by SRS alone would be, at most, ___.” The characteristics of physicians willing to recommend SRS alone for ≥ 5 metastases were assessed. Chi-square was used for univariate analysis, and logistic regression for multivariate analysis.

RESULTS: The final study sample included 95 Gamma Knife and LINAC-using respondents (54% Gamma Knife users) in San Francisco and 54 in Sendai (48% Gamma Knife users). More than 70% at each meeting had ≥ 5 years experience with SRS. Sixty-five percent in San Francisco and 83% in Sendai treated ≥ 30 cases annually with SRS. The highest number of metastases considered reasonable to treat with SRS alone in both surveys was 50. In San Francisco, the mean and median numbers of metastases considered reasonable to treat with SRS alone were 6.7 and 5, while in Sendai they were 11 and 10. In the San Francisco sample, the clinical factors identified to be most influential in decision making were Karnofsky Performance Scale score (78%), presence/absence of mass effect (76%), and systemic disease control (63%). In Sendai, the most influential factors were the size of the metastases (78%), the Karnofsky Performance Scale score (70%), and metastasis location (68%). In San Francisco, 55% of respondents considered treating ≥ 5 metastases and 22% considered treating ≥ 10 metastases “reasonable.” In Sendai, 83% of respondents considered treating ≥ 5 metastases and 57% considered treating ≥ 10 metastases “reasonable.” In both groups, private practitioners, neurosurgeons, and Gamma Knife users were statistically significantly more likely to treat ≥ 5 metastases with SRS alone.

CONCLUSIONS: Although there is no clear consensus for how many metastases are reasonable to treat with SRS alone, more than half of the radiosurgeons at 2 international meetings were willing to extend the use of SRS as an initial treatment for ≥ 5 brain metastases. Given the substantial variation in clinicians' approaches to SRS use, further research is required to identify patient characteristics associated with optimal SRS outcomes.

Gamma knife surgery for 1-10 brain metastases without prophylactic whole-brain radiation therapy: analysis of cases meeting the Japanese prospective multi-institute study (JLGK0901) inclusion criteria.
We evaluated the results of stereotactic radiosurgery (SRS) alone using gamma knife (GK) for selected patients with 1-10 brain metastases without prophylactic whole-brain radiation therapy (WBRT) among JLGK0901-eligible cases. Seven hundred seventy-eight consecutive cases meeting the following JLGK0901 study inclusion criteria were analyzed: (1) newly diagnosed brain metastases, (2) 1-10 brain lesions, (3) less than 10 cm³ volume of the largest tumor, (4) less than 15 cm³ total tumor volume, (5) no magnetic resonance (MR) findings of cerebrospinal fluid (CSF) dissemination, and (6) no impaired activity of daily living (<70 Karnofsky Performance Score (KPS)) due to extracranial disease. At initial treatment, all lesions were irradiated with SRS without upfront WBRT. Thereafter, enhanced magnetic resonance imaging (MRI) was applied every 2-3 months, and new distant lesions were appropriately retreated with SRS or WBRT. We divided patients according to tumor number: single lesion for group A (280 cases), 2 for group B (135), 3-4 for group C (148), 5-6 for group D (93), and 7-10 for group E (122). Differences among groups were compared in terms of overall, neurological, qualitative, and new-lesion-free survival (NLFS). Median age was 65 years (range 26-92 years). There were 505 men and 273 women. The primary organ was lung in 579 patients, gastrointestinal tract in 79, breast in 48, urinary tract in 34, and others/unknown in 38. Mean survival time was 0.72 years (0.83 years for 1, 0.69 years for 2, 0.69 years for 3-4, 0.59 years for 5-6, and 0.62 years for 7-10 metastases). On multivariate analysis, significant poor prognostic factors for overall survival (OS) were active systemic disease, poor (<70) initial KPS, and male gender. Neurological survival and qualitative survival at 1 year were 92.7% and 88.2%, respectively. NLFS at 6 months and 1 year were 69.8% and 43.8%, respectively. There were statistically significant differences in new lesion emergence between groups A and B and between groups B and C. SRS using GK provides excellent results in selected patients with 1-10 brain lesions, without prophylactic WBRT. This study revealed that brain lesion number has no effect on any of the four types of survivals, which is anticipated to be confirmed by the JLGK0901 study.

**CONCLUSIONS:** Patient age and primary tumor control are more important factors in predicting median survival time than number of metastases to the brain. Long-term survivors are more common than previously assumed.

**Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases.**


**PURPOSE:** Multiple brain metastases are a common health problem, frequently diagnosed in patients with cancer. The prognosis, even after treatment with whole brain radiation therapy (WBRT), is poor with average expected survivals less than 6 months. Retrospective series of stereotactic radiosurgery have shown local control and survival benefits in case series of patients with solitary brain metastases. We hypothesized that radiosurgery plus WBRT would provide improved local brain tumor control over WBRT alone in patients with two to four brain metastases.

**METHODS:** Patients with two to four brain metastases (all ≤25 mm diameter and known primary tumor type) were randomized to initial brain tumor management with WBRT alone (30 Gy in 12 fractions) or WBRT plus radiosurgery. Extent of extracranial cancer, tumor diameters on MRI scan, and functional status were recorded before and after initial care.

**RESULTS:** The study was stopped at an interim evaluation at 60% accrual. Twenty-seven patients were randomized (14 to WBRT alone and 13 to WBRT plus radiosurgery). The groups were well matched to age, sex, tumor type, number of tumors, and extent of extracranial disease. The rate of local failure at 1 year was 100% after WBRT alone but only 8% in patients who had boost radiosurgery. The median time to local failure was 6 months after WBRT alone (95% confidence interval [CI], 3.5-8.5) in comparison to 36 months (95% CI, 15.6-57) after WBRT plus radiosurgery (p = 0.0005). The median time to any brain failure was improved in the radiosurgery group (p = 0.002). Tumor control did not depend on histology (p = 0.85), number of initial brain metastases (p = 0.25), or extent of extracranial disease (p = 0.26). Patients who received WBRT alone lived a median of 7.5 months, while those who received WBRT plus radiosurgery lived 11 months (p = 0.22). Survival did not depend on histology or number of tumors, but was related to extent of extracranial disease (p = 0.02). There was no neurologic or systemic morbidity related to stereotactic radiosurgery.

**CONCLUSIONS:** Combined WBRT and radiosurgery for patients with two to four brain metastases significantly improves control of brain disease. WBRT alone does not provide lasting and effective care for most patients.
Cost Effectiveness

Cost-effectiveness Analysis of a Randomized Study Comparing Radiosurgery With Radiosurgery and Whole Brain Radiation Therapy in Patients With 1 to 3 Brain Metastases.

Source*Ingenix Consulting-Healthcare, Missouri City || Division of Pharmacy ¶ Division of Pharmacy, Pharmacy Informatics # Division of Pharmacy, Drug Use Policy and Pharmacoeconomics, University of Texas MD, Anderson Cancer Center ‡ Division of Management, Policy and Community Health, The University of Texas School of Public Health, Houston, TX † Health Economics and Outcomes I3 Innovus, Eden Prairie, MN § Global Health Outcomes, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN.
Am J Clin Oncol. 2011 Feb 2. [Epub ahead of print]

BACKGROUND: In this study, we compare 2 treatment options and determine cost-effectiveness and cost-utility. METHODS: We carried out a decision analysis populated with data from patients with brain metastasis in a concurrent trial randomized to either stereotactic radiosurgery (SRS) and observation or SRS and whole brain radiation therapy. Outcomes included actual life years saved (LYS), quality-adjusted life years (QALYs), and incremental cost-effectiveness ratio (ICER). Costs used were from the healthcare perspective and utilities were captured through a time-trade-off method, using 10-year, 5-year, and 1-year time horizons. One-way sensitivity analyses were carried out to determine robustness of the decision analysis model.

RESULTS: Compared with SRS and whole brain radiation therapy, SRS and observation not only had a higher average cost ($74,000 vs $119,000, respectively) but also a higher average effectiveness (0.60 LYS vs 1.64 LYS, respectively) with an ICER of $44,231/LYS or $41,783/QALY (with utilities captured using a 10-year horizon). Slightly higher ICER estimates were achieved with utilities captured using the other time horizons ($43,280/QALY and $44,064/QALY, respectively). Sensitivity analysis showed that the following variables had the highest impact on the ICER: probability of no recurrence in recursive-partitioning analysis class 2 after SRS and observation; probability of being alive after SRS and observation in recursive-partitioning analysis class 2 and being treated for recurrence.

CONCLUSIONS: Compared with other interventions in the $50,000 to $100,000/QALY cost-effectiveness range, the application of SRS and observation, with subsequent neurosurgical management of recurrences, is shown to be a reasonable treatment modality for brain metastases.

Economic impact of stereotactic radiosurgery for malignant intracranial brain tumors.

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Brain metastases occur frequently in cancer patients and can lead to neurological complications that result in decreased quantity and quality of life. Treatment alternatives include whole-brain radiation therapy, neurosurgery and the newest modality, stereotactic radiosurgery (SRS). This article reviews economic evaluations of SRS in the metastatic setting compared with other treatment options. Studies were included if they were published in peer-reviewed journals, primarily focused on patients with malignant brain metastasis and included a cost analysis between interventions. Uncertainty surrounding the cost-effectiveness of SRS is due to a lack of efficacy information between treatment alternatives, methodological limitations and design differences between the available studies. When cost-effectiveness ratios are available, SRS appears to be a reasonable option in resource-limited settings, with incremental cost-effectiveness ratios just below the US$50,000 range. However, better-designed economic analysis in the setting of randomized clinical trials or observational studies needs to be conducted to fully understand the economic value of SRS.
**A meta-analysis evaluating stereotactic radiosurgery, whole-brain radiotherapy, or both for patients presenting with a limited number of brain metastases.**

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**BACKGROUND:** To perform a meta-analysis on newly diagnosed brain metastases patients treated with whole-brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS) boost versus WBRT alone, or in patients treated with SRS alone versus WBRT and SRS boost.

**METHODS:** The meta-analysis primary outcomes were overall survival (OS), local control (LC), and distant brain control (DBC). Secondary outcomes were neurocognition, quality of life (QOL), and toxicity. Using published Kaplan-Meier curves, results were pooled using hazard ratios (HR).

**RESULTS:** Two RCTs reported on WBRT and SRS boost versus WBRT alone. For multiple brain metastases (2-4 tumors) we conclude no difference in OS, and LC significantly favored WBRT plus SRS boost. Three RCTs reported on SRS alone versus WBRT plus SRS boost (1-4 tumors). There was no difference in OS despite both LC and DBC significantly favoring WBRT plus SRS boost. Although secondary endpoints could not be pooled for meta-analysis, those RCTs evaluating SRS alone conclude better neurocognition using the validated Hopkins Verbal Learning Test, no adverse risk in deteriorating Mini-Mental Status Exam scores or in maintaining performance status, and fewer late toxicities. We conclude insufficient data for QOL outcomes.

**CONCLUSIONS:** For selected patients, we conclude no OS benefit for WBRT plus SRS boost compared with SRS alone. Although additional WBRT improves DBC and LC, SRS alone should be considered a routine treatment option due to favorable neurocognitive outcomes, less risk of late side effects, and does not adversely affect the patients performance status.

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**Management of cerebral metastasis: evidence-based approach for surgery, stereotactic radiosurgery and radiotherapy.**

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Brain metastases constitute a significant disease burden and have a major impact on morbidity and mortality. This review discusses the relative merits of open surgery, whole brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS), which have been used alone and in combination with varying degrees of success for the treatment of newly diagnosed brain metastasis. Treatment aims to provide disease control with a good quality of life, although prolonged survival may not always be achieved. Decision to treat is based on several prognostic factors including age, performance status and control of the primary cancer. The recently developed disease-specific graded prognostic assessment (DS-GPA) scales can aid in clinical decision making for individual patients. Whole brain radiotherapy remains the mainstay of treatment and provides effective palliation. Omission of WBRT results in worse local and distant control, though not survival. Local tumour control can be achieved by either resection of stereotactic radiosurgery (SRS). In long-term survivors WBRT may cause cognitive decline and SRS is being explored as an alternative method of disease control. Increasingly, quality of life and neuro-cognitive function are being used as end-points in clinical trials.

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**Local control of newly diagnosed and distally recurrent, low-volume brain metastases with fixed-dose (20 gy) gamma knife radiosurgery.**

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**BACKGROUND:** Metastases to the brain occur in 20% to 30% of patients with cancer and have been identified on autopsy in as many as 50% of patients.

**OBJECTIVE:** To analyze the efficacy of 20-Gy Gamma Knife radiosurgery (GKR) as initial treatment in patients with 1 to 3 brain metastases ≤ 2 cm in greatest diameter.
METHODS: A retrospective analysis of 114 consecutive adults with Karnofsky performance status ≥ 60 who received GKR for 1 to 3 brain metastases ≤ 2 cm in size was performed. Five patients lacked detailed follow-up and were excluded, leaving 109 for outcome analysis (34 men and 75 women; median age, 61.2 years). All metastases received 20 Gy to the 50% isodose line.

RESULTS: One hundred nine patients underwent treatment of 164 metastases at initial GKR. Twenty-six patients (23.9%) were alive at last follow-up (median time, 29.9 months; range, 6.6 months to 7.8 years). The median overall survival was 13.8 months (range, 1 day to 7.6 years). Among the 52 patients with distant failure, 33 patients received 20 Gy to 95 new lesions. A total of 259 metastases received 20 Gy, and 4 patients lacked imaging follow-up secondary to death before posttreatment imaging. Local failure occurred in 17 of 255 treated lesions (6.7%), yielding an overall local control rate of 93.3%. Actuarial local control at 6, 12, 24, and 36 months was 96%, 93%, 89%, and 88%, respectively. Permanent neurological complications occurred in 3 patients (2.8%).

CONCLUSION: Among patients with 1 to 3 brain metastases ≤ 2 cm in size who have not received whole-brain radiation therapy, GKR with 20 Gy provides high rates of local control with low morbidity and excellent neurological symptom-free survival.

Timing and risk factors for new brain metastasis formation in patients initially treated only with Gamma Knife surgery. Clinical article.

OBJECT: Stereotactic radiosurgery has been shown to afford a reasonable chance of local tumor control. However, new brain metastasis can arise following successful local tumor control from radiosurgery. This study evaluated the timing, number, and risk factors for development of subsequent new brain metastasis in a group of patients treated with stereotactic radiosurgery alone.

METHODS: One hundred seventeen patients with histologically confirmed metastatic cancer underwent Gamma Knife surgery (GKS) to treat all brain metastases demonstrable on MR imaging. Patients were followed clinically and radiologically at approximately 3-month intervals for a median of 14.4 months (range 0.37-51.8 months). Follow-up MR images were evaluated for evidence of new brain metastasis formation. Statistical analyses were performed to determine the timing, number, and risk factors for development of new brain metastases.

RESULTS: The median time to development of a new brain metastasis was 8.8 months. Patients with 3 or more metastases at the time of initial radiosurgery or those with cancer histologies other than non-small cell lung carcinoma were found to be at increased risk for early formation of new brain metastasis (p < 0.05). The mean number of new metastases per patient was 1.6 (range 0-11). Those with a higher Karnofsky Performance Scale score at the time of initial GKS were significantly more likely to develop a greater number of brain metastases by the last follow-up evaluation.

CONCLUSIONS: The timing and number of new brain metastases developing in patients treated with GKS alone is not inconsequential. Those with 3 or more metastases at the time of radiosurgery and those with cancer histology other than non-small cell lung carcinoma were at greater risk of early formation of new brain metastasis. Frequent follow-up evaluations, such as at 3-month intervals, appears appropriate in this patient population, particularly in high-risk patients. When detected early, salvage treatments including repeat radiosurgery can be used to treat new brain metastasis.

Thirty years' experience with Gamma Knife surgery for metastases to the brain.

OBJECT: The aim of this study was to analyze factors influencing survival time and patterns of distant recurrences after Gamma Knife surgery (GKS) for metastases to the brain.

METHODS: Information was available for 1855 of 1921 patients who underwent GKS for single or multiple cerebral metastases at 4 different institutions during different time periods between 1975 and 2007. The total number of Gamma Knife treatments administered was 2448, an average of 1.32 treatments per patient. The median survival time was analyzed, related to patient and treatment parameters, and compared with published data following conventional fractionated whole-brain irradiation.

RESULTS: Twenty-five patients survived for longer than 10 years after GKS, and 23 are still alive. Age and primary tumor control were strongly related to survival time. Patients with single metastases had a longer survival than those with multiple metastases, but there was no difference in survival between patients with single and multiple
metastases who had controlled primary disease. There were no significant differences in median survival time between patients with 2, 3-4, 5-8, or >8 metastases. The 5-year survival rate was 6% for the whole patient population, and 9% for patients with controlled primary disease. New hematogenous spread was a more significant problem than micrometastases in patients with longer survival.

A multi-institutional experience with stereotactic radiosurgery for solitary brain metastasis.


PURPOSE: A multi-institutional experience in radiosurgery for solitary brain metastases was combined to identify factors associated with safety, efficacy, tumor control, and survival.

MATERIALS AND METHODS: A review of 116 patients with solitary brain metastases who underwent gamma knife stereotactic radiosurgery at five institutions was performed. The median follow-up was 7 months following radiosurgery and 12 months following diagnosis. Minimum tumor doses varied from 8-30 Gy (mean, 17.5 Gy). Forty-five patients failed prior radiotherapy and 71 had no prior brain irradiation. Fifty-one patients had radiosurgery alone and 65 underwent combined radiosurgery with fractionated large-field radiotherapy (mean dose, 33.8 Gy).

RESULTS: Median survival was 11 months after radiosurgery and 20 months after diagnosis. Follow-up documented local tumor control in 99 patients (85%), tumor recurrence in 17 (15%), and documented radiation necrosis in one (1%). The 2-year actuarial tumor control rate was 67 +/- 8%. Tumor histology affected survival (better for breast cancer, p = .004) and local control (better for melanoma and renal cell, p = .0003) in multivariate analyses. Combined fractionated radiotherapy and radiosurgery improved local control (p = 0.111), but not survival in multivariate testing.

CONCLUSION: Radiosurgery is effective in controlling solitary brain metastases with low morbidity. Further study is needed to better define optimum treatment parameters for radiosurgery.

Defining the role of radiosurgery in the management of brain metastases.


The role of stereotactic radiosurgery in the management of recurrent and newly diagnosed brain metastases was evaluated prospectively. From December 1988 to March 1991, 58 lesions in 40 patients were treated with accelerator-based stereotactic radiosurgery. All patients were followed for a minimum of 6 months or to death. The primary purpose was to determine the impact of radiosurgery on local control and its subsequent effects on quality of life. An overall tumor control rate of 82% with a complete response rate of 43% were achieved. As anticipated, the response rate for smaller tumors was substantially better than that for larger tumors (78% for lesions < 2 cm3; 50% for lesions ≥ 10 cm3). Although the overall in-field progression rate was 18.5%, only 1/23 (4%) complete responders subsequently recurred. The in-field failure rate is highly comparable with recently published surgical data. Progression outside the brain was noted in two-thirds of patients. One quarter of the deaths were neurologic. The median survival for this minimally selected patient population was 6.5 months. Stereotactic radiosurgery was also associated with improved quality of life as measured by Karnofsky score, neurologic function, and steroid dependence. Long-term steroid dependence was encountered in only four patients. We conclude that stereotactic radiosurgery can be used effectively in patients with brain metastases. In this series, a high tumor response rate was achieved which was associated with improved quality of life.
Clinical Guidelines

The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline.

QUESTION: Should patients with newly-diagnosed metastatic brain tumors undergo stereotactic radiosurgery (SRS) compared with other treatment modalities?

TARGET POPULATION: These recommendations apply to adults with newly diagnosed solid brain metastases amenable to SRS; lesions amenable to SRS are typically defined as measuring less than 3 cm in maximum diameter and producing minimal (less than 1 cm of midline shift) mass effect.

RECOMMENDATIONS

• **SRS plus WBRT vs. WBRT alone**
  Level 1 Single-dose SRS along with WBRT leads to significantly longer patient survival compared with WBRT alone for patients with single metastatic brain tumors who have a KPS > or = 70.
  Level 1 Single-dose SRS along with WBRT is superior in terms of local tumor control and maintaining functional status when compared to WBRT alone for patients with 1-4 metastatic brain tumors who have a KPS > or =70.
  Level 2 Single-dose SRS alone may provide an equivalent survival advantage for patients with brain metastases compared with WBRT + single-dose SRS.
  There is conflicting class I and II evidence regarding the risk of both local and distant recurrence when SRS is used in isolation, and class I evidence demonstrates a lower risk of distant recurrence with WBRT; thus, regular careful surveillance is warranted for patients treated with SRS alone in order to provide early identification of local and distant recurrences so that salvage therapy can be initiated at the soonest possible time.

• **Surgical Resection plus WBRT vs. SRS +/- WBRT**
  Level 2 Surgical resection plus WBRT, vs. SRS plus WBRT, both represent effective treatment strategies, resulting in relatively equal survival rates.
  SRS has not been assessed from an evidence-based standpoint for larger lesions (>3 cm) or for those causing significant mass effect (>1 cm midline shift).
  Level 3: Underpowered class I evidence along with the preponderance of conflicting class II evidence suggests that SRS alone may provide equivalent functional and survival outcomes compared with resection + WBRT for patients with single brain metastases, so long as ready detection of distant site failure and salvage SRS are possible.

• **SRS alone vs. WBRT alone**
  Level 3 While both single-dose SRS and WBRT are effective for treating patients with brain metastases, single-dose SRS alone appears to be superior to WBRT alone for patients with up to three metastatic brain tumors in terms of patient survival advantage.
Prognostic Variables/Models

What factors predict the response of larger brain metastases to radiosurgery?
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BACKGROUND: Approximately 20 to 40% of patients with systemic malignancies develop brain metastases.

OBJECTIVE: To assess the potential role of stereotactic radiosurgery (SRS) for larger metastatic brain tumors, we reviewed our recent experience.

METHODS: Between 2004 and 2008, 70 patients with a metastatic brain tumor larger than 3 cm in maximum diameter underwent Gamma knife SRS. Thirty-three patients had received previous whole brain radiation therapy (WBRT) and 37 received only SRS.

RESULTS: The overall median follow-up was 8.1 months. At the first planned imaging follow-up at 2 months, 29 (41%) tumors had >50% volume reduction, 22 (31%) had 10 to 50% volume reduction, and 19 (28%) were stable or larger. We also evaluated brain edema using MRI T2 images. In 11 patients (16%) the peritumoral edema volume was reduced by more than 50%, in 25 (36%) it was reduced by 10 to 50%, in 21 (30%) it was stable, and in 13 (19%) it was increased. Twenty (36%) discontinued corticosteroids by the time of first imaging follow-up. Because of persistent symptoms, 7 patients (10%) required a craniotomy to remove the tumor. Tumor volume reduction (>50%) was associated with a single metastasis (P=.012), no previous WBRT (P=.002), and a tumor volume<16 cm3 (P=.002). The better peritumoral edema volume reduction (>50%) was associated with a single metastasis (P=.024), no previous WBRT (P=.05), and breast cancer histology (P=.044).

CONCLUSION: Surgical resection remains the primary approach for larger brain metastases if feasible. Tumor volume is a better indicator than maximum diameter. Tumor volume and edema responded better in patients who underwent SRS alone.

Validity of the graded prognostic assessment-derived index to predict brain-metastatic patients' survival after Gamma Knife radiosurgery.
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PURPOSE: To appraise whether the graded prognostic assessment (GPA)-derived index is valid for selecting patients with brain metastases for Gamma Knife (GK) radiosurgery.

METHODS AND MATERIALS: A total of 56 consecutive patients in recursive partioning analysis (RPA) Class I (n = 19, 34%) and II (n = 37, 66%) formed the basis of this retrospective study. Their mean age was of 57 years with mean Karnofsky performance score of 77. Primary cancers stemmed mainly from the lungs (59%). A total of 45 patients (80%) harbored multiple tumors. The mean clinical follow-up period was 9 months.

RESULTS: Kaplan-Meier analysis demonstrated that the overall median survival time (MST) for the whole series was 11.5 months: 16.5 vs. 6.5 months for RPA class I and II (p = 0.017). Multivariate Cox analysis revealed that female patients and a pre-GK good functional state were favorable prognostic factors. The favorable MST was in patients with a GPA score of 3 to 4 (17 months) followed by a GPA score of 2 to 2.5 (11 months) and GPA score 0 to 1.5 (6.5 months), but without statistical differences (p = 0.413) in between. A modified index (MGPA) is proposed with gender as a cofactor, then there existed a distinct survival differences (p = 0.028) between patients with an MGPA score of 3.5 to 5 (15 months) and with an MGPA score of 0 to 3 (7 months). In addition, the original GPA index failed to imply the difference of MST in patients with lung origin.

CONCLUSIONS: The GPA-derived index is not applicable to our set of patients for comparing their survival after GK radiosurgery. The gender of the patients is a suggested cofactor to further refine the greater prognostic accuracy of the GPA index.

Survival and pattern of failure in brain metastasis treated with stereotactic gamma knife radiosurgery.

OBJECT: Gamma knife radiosurgery (GKS) has become a well-established treatment modality in the management of selected patients with brain metastasis. The authors review the management patients with these tumors
treated at a single center.

**METHODS:** Between 1994 and 2002, 458 consecutive patients with metastatic brain disease underwent GKS. There were 1305 lesions treated in 680 separate sessions. 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%), unknown primary site in 14 (3.1%), and other in 39 patients (8.5%). The median tumor volume was 0.9 cm³ and the median volume treated was 2.3 cm³. The median radiation dose was 18 Gy prescribed to a median isodose of 60%; the median dose was 20 Gy in melanoma, sarcoma, and RCC. Whole-brain radiotherapy (WBRT) either prior to or following GKS was performed in 114 patients (25%). Follow up ranged from 3 to 84 months with a median of 9 months. The median survival for all patients was 9 months and depended on tumor histology. Survival ranged from 6 months for patients with colon carcinoma, unknown primary tumors, and other tumors to 17 months for those with breast cancer. The median survival for patients with melanoma was 8 months. In multivariate analysis, Karnofsky Performance Scale score (< 70 vs > 70), status of systemic disease (yes vs no), histological diagnosis, and total intracranial tumor volume were the only significant factors influencing survival. The number of brain metastases (one-five), WBRT (yes vs no), and age were not significant. Pattern of failure was different in patients with melanoma compared with those with other diagnoses. Cause of death in patients with melanoma was in 50% of the cases due to systemic disease and in 42% due to central nervous system causes, whereas it was 70% for the former and 23% for the latter in patients with other diagnoses. The treatment was well tolerated with significant late toxicity requiring craniotomy for removal of a necrotic focus in only 20 patients (4.7%).

**CONCLUSIONS:** Gamma knife radiosurgery provided an excellent palliation with low incidence of toxicity. A Phase III prospective randomized trial is required to define the role of WBRT in combination with GKS.

**Radiosurgery for patients with brain metastases: a multi-institutional analysis, stratified by the RTOG recursive partitioning analysis method.**

*Sanghavi SN, Miranpuri SS, Chappell R, Buatti JM, Sneed PK, Suh JH et al. (2001)*


**PURPOSE:** To estimate the potential improvement in survival for patients with brain metastases, stratified by the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) class and treated with radiosurgery (RS) plus whole brain radiotherapy (WBRT).

**METHODS AND MATERIALS:** An analysis of the RS databases of 10 institutions identified patients with brain metastases treated with RS and WBRT. Patients were stratified into 1 of 3 RPA classes. Survival was evaluated using Kaplan-Meier estimates and proportional hazard regression analysis. A comparison of survival by class was carried out with the RTOG results in similar patients receiving WBRT alone.

**RESULTS:** Five hundred two patients were eligible (261 men and 241 women, median age 59 years, range 26–83). The overall median survival was 10.7 months. A higher Karnofsky performance status (p = 0.0001), a controlled primary (median survival = 11.6 vs. 8.8 months, p = 0.0023), absence of extracranial metastases (median survival 13.4 vs. 9.1 months, p = 0.0001), and lower RPA class (median survival 16.1 months for class I vs. 10.3 months for class II vs. 8.7 months for class III, p = 0.000007) predicted for improved survival. Gender, age, primary site, radiosurgery technique, and institution were not prognostic. The addition of RS boosted results in median survival (16.1, 10.3, and 8.7 months for classes I, II, and III, respectively) compared with the median survival (7.1, 4.2, and 2.3 months, p <0.05) observed in the RTOG RPA analysis for patients treated with WBRT alone.

**CONCLUSION:** In the absence of randomized data, these results suggest that RS may improve survival in patients with BM. The improvement in survival does not appear to be restricted by class for well-selected patients.

**Application of recursive partitioning analysis and evaluation of the use of whole brain radiation among patients treated with stereotactic radiosurgery for newly diagnosed brain metastases.**

*Chidel MA, Suh JH, Reddy CA, Chao ST, Lundbeck MF, Barnett GH (2000)*


**PURPOSE:** To evaluate the usefulness of whole brain radiotherapy (WBRT) and of the Radiation Therapy Oncology Group recursive partitioning analysis (RPA) for brain metastases among patients receiving stereotactic radiosurgery (SRS).

**METHODS AND MATERIALS:** A retrospective analysis was performed on 135 patients who underwent linear accelerator (Linac) (n = 73) or Gamma Knife (n = 62) SRS for newly diagnosed brain metastases at the Cleveland Clinic Foundation between 8/89 and 12/98. Univariate and multivariate analyses were performed to evaluate the effects of age, primary site, control of the primary, interval to development of brain metastases (disease-free
interval [DFI]), number of brain metastases, presence of extracranial metastases, Karnofsky performance status (KPS), treatment of brain metastases, and RPA class on overall survival.

**RESULTS:** Application of the RPA classification revealed 29 patients fit the criteria for class I, 96 for class II, and 10 for class III. All of the patients underwent SRS. Fifty-seven patients also received WBRT at the time of initial presentation (SRS and immediate WBRT), and 78 patients received WBRT only if CNS relapse occurred (SRS alone). The median survival for all patients was 7.9 months (range: 1.1-90.1), and was 11.2 months for RPA class I compared to 6.9 months for RPA classes II-III (p = 0.016). Median survival was 10.5 months following SRS alone compared to 6.4 months following SRS and WBRT (p = 0.07). On univariate analysis, KPS >/= 80% (p = 0.002) and absence of systemic disease (p = 0.013) were also associated with longer survival, whereas control of the primary, DFI, and number of brain metastases did not have an impact. Multivariate analysis revealed only RPA class (p = 0.023) to be an independent predictor for overall survival, whereas treatment group (p = 0.079) was only marginally significant. At 2 years, immediate WBRT improved control at the original site of metastases (80% vs. 52%, p = 0.03) and prevention of new metastatic sites within the brain, 74% vs. 48% (p = 0.06). The 2-year intracranial disease-free survival was 60% following SRS and WBRT compared to only 34% following SRS alone (p = 0.03).

**CONCLUSIONS:** Despite the inherent biases to select more favorable patients for SRS, the RPA class retains its prognostic value. Omission of WBRT from the initial management was not detrimental in terms of overall survival; however, progressive disease occurred in over 50% of patients treated in this manner. Further studies are required to determine which, if any, patients should be considered for SRS with WBRT held in reserve.

*Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials.*

**PURPOSE:** Promising results from new approaches such as radiosurgery or stereotactic surgery of brain metastases have recently been reported. Are these results due to the therapy alone or can the results be attributed in part to patient selection? An analysis of tumor/patient characteristics and treatment variables in previous Radiation Therapy Oncology Group (RTOG) brain metastases studies was considered necessary to fully evaluate the benefit of these new interventions.

**METHODS AND MATERIALS:** The database included 1200 patients from three consecutive RTOG trials conducted between 1979 and 1993, which tested several different dose fractionation schemes and radiation sensitizers. Using recursive partitioning analysis (RPA), a statistical methodology which creates a regression tree according to prognostic significance, eighteen pretreatment characteristics and three treatment-related variables were analyzed.

**RESULTS:** According to the RPA tree the best survival (median: 7.1 months) was observed in patients < 65 years of age with a Karnofsky Performance Status (KPS) of at least 70, and a controlled primary tumor with the brain the only site of metastases. The worst survival (median: 2.3 months) was seen in patients with a KPS less than 70. All other patients had relatively minor differences in observed survival, with a median of 4.2 months.

**CONCLUSIONS:** Based on this analysis, we suggest the following three classes: Class 1: patients with KPS > or = 70, < 65 years of age with controlled primary and no extracranial metastases; Class 3: KPS < 70; Class 2- all others. Using these classes or stages, new treatment techniques can be tested on homogeneous patient groups.
Diagnostic Imaging

Detection of brain micrometastases by high-resolution stereotactic magnetic resonance imaging and its impact on the timing of and risk for distant recurrences.
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OBJECT The aim of this study was to assess the order of micrometastases that can be detected with high-resolution MR imaging at the time of Gamma Knife surgery (GKS), and to estimate the impact this has on the time until and incidence of distant recurrences.

METHODS A consecutive series of 835 patients with brain metastases treated with GKS in a 7-year period, excluding patients in whom earlier brain metastases were treated with other modalities, were retrospectively analyzed. In all patients GKS was based on high Gd-dose (0.3 mmol/kg), high-resolution stereotactic MR imaging. These images were compared with the standard pretreatment MR images, and the difference in number of metastases found was analyzed. The distant recurrence rate following GKS was compared with that found in a prospective randomized study (Aoyama et al.) comparing radiosurgery to radiosurgery plus prophylactic whole-brain radiation therapy.

RESULTS New tumors were diagnosed in 40% (95% CI 36%-43%) of all patients as well as in the majority of patients with multiple lesions found on the diagnostic scan. The more tumors there were on the diagnostic scan, the higher the likelihood of detecting additional lesions with high-resolution imaging. It was calculated that approximately 50% of the micrometastases present at the time of GKS could be diagnosed with high-resolution imaging, which decreased the incidence of and delayed the time for the development of distant recurrences.

CONCLUSIONS Additional brain metastases can be diagnosed in 40% of patients by using high-resolution imaging. Thus, radiosurgical treatments based on high-resolution stereotactic MR imaging decrease the incidence of and lengthen the time to distant recurrences.

Clinical application of 7.0 T magnetic resonance images in Gamma Knife radiosurgery for a patient with brain metastases.
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In the study we assessed the distortion of 7.0 T magnetic resonance (MR) images in reference to 1.5 T MR images in the radiosurgery of metastatic brain tumors. Radiosurgery with Gamma Knife Perfexion was performed for the treatment of a 54-yr-old female patient with multiple brain metastases by the co-registered images of the 7.0 T and 1.5 T magnetic resonance images (MRI). There was no significant discrepancy in the positions of anterior and posterior commissures as well as the locations of four metastatic brain tumors in the co-registered images between 7.0 T and 1.5 T MRI with better visualization of the anatomical details in 7.0 T MR images. This study demonstrates for the first time that 7.0 T MR images can be safely utilized in Perfexion Gamma Knife radiosurgery for the treatment of metastatic brain tumors. Furthermore 7.0 T MR images provide better visualization of brain tumors without image distortion in comparison to 1.5 T MR images.

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J Neurooncol. 2011 Apr 27. [Epub ahead of print]

To determine the safety, tolerability, and report on secondary efficacy endpoints of motexafin gadolinium (Mgd) in combination with whole-brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS) for patients with ≤6 brain metastases. We conducted an international study of WBRT (37.5 Gy in 15 fractions) and SRS (15-21 Gy) with the addition of Mgd (5 mg/kg preceding each fraction beginning week 2). The primary endpoint was to evaluate
the rate of irreversible grade 3 or any grade ≥4 neurotoxicity and establish feasibility in preparation for a phase III trial. Sixty-five patients were enrolled from 14 institutions, of which 45 (69%) received SRS with MGD as intended and were available for evaluation. Grade ≥3 neurotoxicity attributable to radiation therapy within 3 months of SRS was seen in 2 patients (4.4%), including generalized weakness and radionecrosis requiring surgical management. Immediately following the course of MGD plus WBRT, new brain metastases were detected in 11 patients (24.4%) at the time of the SRS treatment planning MRI. The actuarial incidence of neurologic progression at 6 months and 1 year was 17 and 20%, respectively. The median investigator-determined neurologic progression free survival and overall survival times were 8 (95% CI: 5-14) and 9 months (95% CI: 6-not reached), respectively. We observed a low rate of neurotoxicity, demonstrating that the addition of MGD does not increase the incidence or severity of neurologic complications from WBRT with SRS boost.

**Increases in the number of brain metastases detected at frame-fixed, thin-slice MRI for gamma knife surgery planning.**


For gamma knife planning, 2.4-mm-slice MRIs are taken under rigid frame fixation, so tiny tumors become visible. This study evaluated differences in the numbers of brain metastases between conventional contrast-enhanced MRI (6 ± 1 mm slice thickness) taken before patient referral and contrast-enhanced MRI for gamma knife planning. The numbers of metastases on the 2 images were counted by at least 2 oncologists. For gamma knife planning, spoiled gradient-recalled echo images were obtained after 0.1 mmol/kg gadolinium administration using a 1.5-T system. Images from 1045 patients with an interval between the 2 MRI studies of 6 weeks or less were analyzed. Increases in the number of metastases were found in 33.7% of the 1045 patients, whereas the number was identical in 62.3%. In 4.0%, the number decreased, indicating overdiagnosis at conventional MRI. These proportions did not differ significantly by the interval before gamma knife. An increase from single to multiple metastases was found in 16.0%. Meningeal dissemination was newly diagnosed in 2.3%. On planning images, the proportions of patients with 1, 2, 3, and 4 or more lesions were 37.6%, 19.3%, 9.3%, and 33.8%, respectively. In cases of colorectal cancer and hepatoma, the proportions of patients with a single metastasis (32 of 61 [52%] and 5 of 6 [83%], respectively) were higher than that of patients with other malignancies. In about one-third of the patients, an increased number of metastases were found on the thin-slice images. This should be kept in mind when deciding the treatment strategy for brain metastases.
Radiosurgery After Resection

Cavity-directed radiosurgery as adjuvant therapy after resection of a brain metastasis.

OBJECT: As a strategy to delay or avoid whole-brain radiotherapy (WBRT) after resection of a brain metastasis, the authors used high-resolution MR imaging and cavity-directed radiosurgery for the detection and treatment of further metastases.

METHODS: Between April 2001 and October 2009, 112 resection cavities in 106 patients with no prior WBRT were treated using radiosurgery directed to the tumor cavity and for any synchronous brain metastases detected on high-resolution MR imaging at the time of radiosurgical planning. A median dose of 17 Gy to the 50% isodose line was prescribed to the gross tumor volume, defined as the rim of enhancement around the resection cavity. Patients were followed up via serial imaging, and new brain metastases were generally treated using additional radiosurgery, with salvage WBRT typically reserved for local treatment failure at a resection cavity, numerous failures, or failures occurring at short time intervals. Local and distant treatment failures were determined based on imaging results. Kaplan-Meier curves were generated to estimate local and distant treatment failure rates, overall survival, neurological cause-specific survival, and time delay to salvage WBRT.

RESULTS: Radiosurgery was delivered to the resection cavity alone in 57.5% of patients, whereas 24.5% of patients also received treatment for 1 synchronous metastasis, 11.3% also received treatment for 2 synchronous metastases, and 6.6% also received treatment for 3-10 additional lesions. The median overall survival was 10.9 months. Overall survival at 1 year was 46.8%. The local tumor control rate at 1 year was 80.3%. The disease control rate in distant regions of the brain at 1 year was 35.4%, with a median time of 6.9 months to distant failure. Thirty-nine of 106 patients eventually received salvage WBRT, and the median time to salvage WBRT was 12.6 months. Kaplan-Meier estimates showed that the rate of requisite WBRT at 1 year was 45.9%. Neurological cause-specific survival at 1 year was 50.1%. Leptomeningeal failure occurred in 8 patients. One patient had treatment failure within the resection tract. Seven patients required reoperation: 2 for resection cavity recurrence, 3 for radiation necrosis, 1 for hydrocephalus, and 1 for a CSF cutaneous fistula. On multivariate analysis, a preoperative tumor diameter > 3 cm was predictive of local treatment failure.

CONCLUSIONS: Cavity-directed radiosurgery combined with high-resolution MR imaging detection and radiosurgical treatment of synchronous brain metastases is an effective strategy for delaying and even foregoing WBRT in most patients. This technique provides acceptable local disease control, although distant treatment failure remains significant.

Repeat Radiosurgery

Does the surgical resection of a brain metastasis alter the planning and subsequent local control achieved with radiosurgery prescribed for recurrence at the operated site?

Multiple treatments may be used in the management of patients with brain metastases including surgical resection or radiosurgery. In order to determine whether initial surgical resection in any way prejudices the subsequent efficacy of radiosurgery for recurrence at the operated site, a retrospective review of patients undergoing radiosurgery at the time of relapse was undertaken. All patients had previously received whole brain irradiation as part of initial management. A comparison of radiosurgical planning technique was made for recurrent brain metastases occurring at sites of a previous surgical resection versus unresected recurrences. Although recurrences of tumour at a resected site were more likely to be treated radiosurgically using larger and multiple collimators, there was no significant difference in subsequent local control. Assuming that the recurrence of a brain metastasis at a previously resected site is considered treatable radiosurgically, subsequent local control is no different from that achieved in previously unresected recurrences.