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Leksell Gamma Knife[®] Radiosurgery Bibliography

Brain Metastases

2012–2020

≥ 30 patient cohorts

[1] Tumor Control Probability of Radiosurgery and Fractionated Stereotactic Radiosurgery for Brain Metastases.

Int J Radiat Oncol Biol Phys. 2020 Dec 31. pii: S0360-3016(20)34451-5. Redmond KJ, Gui C, Benedict S, Milano MT, Grimm J, Vargo JA, Soltys SG, Yorke E, Jackson A, El Naqa I, Marks LB, Xue J, Heron DE, Kleinberg LR PMID: 33390244 DOI: 10.1016/j.ijrobp.2020.10.034

PURPOSE: As part of the American Association of Physicists in Medicine Working Group on Stereotactic Body Radiotherapy, tumor control probability (TCP) after stereotactic radiosurgery (SRS) and fractionated stereotactic radiosurgery (fSRS) for brain metastases was modeled based on pooled dosimetric and clinical data from published English-language literature. **METHODS AND MATERIALS:** PubMed-indexed studies published between January 1995 and September 2017 were used to evaluate dosimetric and clinical predictors of TCP after SRS or fSRS for brain metastases. Eligible studies had ≥ 10 patients and included detailed dose-fractionation data with corresponding ≥ 1 -year local control (LC) data, typically evaluated as a $>20\%$ increase in diameter of the targeted lesion using the pre-SRS diameter as a reference. **RESULTS:** Of 2951 potentially eligible manuscripts, 56 included sufficient dose-volume data for analyses. Accepting that necrosis and pseudoprogression can complicate the assessment of LC, for tumors ≤ 20 mm, single-fraction doses of 18 and 24 Gy corresponded with $>85\%$ and 95% 1-year LC rates, respectively. For tumors 21 to 30 mm, an 18 Gy single-fraction dose was associated with 75% LC. For tumors 31 to 40 mm, a 15 Gy single-fraction dose yielded approximately 69% LC. For 3- to 5-fraction fSRS using doses in the range of 27 to 35 Gy, 80% 1-year LC has been achieved for tumors of 21 to 40 mm in diameter. **CONCLUSIONS:** TCP for SRS and fSRS are presented. For small lesions ≤ 20 mm, single doses of approximately 18 Gy appear generally associated with excellent rates of LC; for melanoma, higher doses seem warranted. For larger lesions >20 mm, local control rates appear to be approximately 70% to 75% with usual doses of 15 to 18 Gy, and in this setting, fSRS regimens should be considered. Greater consistency in reporting of dosimetric and LC data is needed to facilitate future pooled analyses. As systemic and biologic therapies evolve, updated analyses will be needed to further assess the necessity, efficacy, and toxicity of SRS and fSRS.

[2] Internal dose escalation associated with increased local control for melanoma brain metastases treated with stereotactic radiosurgery.

J Neurosurg. 2020 Dec 11:1-7. Kennedy WR, DeWees TA, Acharya S, Mahmood M, Knutson NC, Goddu SM, Kavanaugh JA, Mitchell TJ, Rich KM, Kim AH, Leuthardt EC, Dowling JL, Dunn GP, Chicoine MR, Perkins SM, Huang J, Tsien CI, Robinson CG, Abraham CD PMID: 33307528 DOI: 10.3171/2020.7.JNS192210

OBJECTIVE: The internal high-dose volume varies widely for a given prescribed dose during stereotactic radiosurgery (SRS) to treat brain metastases (BMs). This may be altered during treatment planning, and the authors have previously shown that this improves local control (LC) for non-small cell lung cancer BMs without increasing toxicity. Here, they seek to identify potentially actionable dosimetric predictors of LC after SRS for melanoma BM. **METHODS:** The records of patients with unresected melanoma BM treated with single-fraction Gamma Knife RS between 2006 and 2017 were reviewed. LC was assessed on a per-lesion basis, defined as stability or a decrease in lesion size. Outcome-oriented approaches were utilized to determine optimal dichotomization for dosimetric variables relative to LC. Univariable and multivariable Cox regression analysis was implemented to evaluate the impact of collected parameters on LC. **RESULTS:** Two hundred eighty-seven melanoma BMs in 79 patients were identified. The median age was 56 years (range 31-86 years). The median follow-up was 7.6 months (range 0.5-81.6 months), and the median survival was 9.3 months (range 1.3-81.6 months). Lesions were optimally stratified by volume receiving at least 30 Gy (V30) greater than or equal to versus less than 25%. V30 was $\geq 25\%$ and $< 25\%$ in 147 and 140 lesions, respectively. For all patients, 1-year LC was 83% versus 66% for V30 $\geq 25\%$ and $< 25\%$, respectively ($p = 0.001$). Stratifying by volume, lesions 2 cm or less ($n = 215$) had 1-year LC of 82% versus 70% ($p = 0.013$) for V30 $\geq 25\%$ and

$< 25\%$, respectively. Lesions > 2 to 3 cm ($n = 32$) had 1-year LC of 100% versus 43% ($p = 0.214$) for V30 $\geq 25\%$ and $< 25\%$, respectively. V30 was still predictive of LC even after controlling for the use of immunotherapy and targeted therapy. Radionecrosis occurred in 2.8% of lesions and was not significantly associated with V30. **CONCLUSIONS:** For a given prescription dose, an increased internal high-dose volume, as indicated by measures such as V30 $\geq 25\%$, is associated with improved LC but not increased toxicity in single-fraction SRS for melanoma BM. Internal dose escalation is an independent predictor of improved LC even in patients receiving immunotherapy and/or targeted therapy. This represents a dosimetric parameter that is actionable at the time of treatment planning and warrants further evaluation.

[3] Dosimetric predictors of symptomatic radiation necrosis after five-fraction radiosurgery for brain metastases.

Radiother Oncol. 2020 Dec 10. pii: S0167-8140(20)31230-5. Andruska N, Kennedy WR, Bonestroo L, Anderson R, Huang Y, Robinson CG, Abraham C, Tsien C, Knutson N, Rich KM, Spencer C, Huang J PMID: 33310010 DOI: 10.1016/j.radonc.2020.12.011

BACKGROUND: To identify factors predictive of developing symptomatic radiation necrosis (sRN) among patients with either intact or resected brain metastases undergoing five-fraction stereotactic radiosurgery (5fSRS). **METHODS:** Multi-institutional retrospective review of 117 brain metastases from 83 patients treated with 5fSRS. The cumulative incidence of sRN and predictors of sRN were calculated using Gray's competing risks and Cox regression. **RESULTS:** The median dose of 5fSRS was 30 Gy (range: 25-40), and 21 lesions (18%) had prior SRS. After a median follow-up of 10.3 months (range: 3-52), the cumulative sRN incidence was 15%, with a median time to sRN of 6.9 months (range: 1.8-31.7). sRN incidence was significantly higher among the lesions treated with prior SRS: hazard ratio (HR): 7.48 [95% confidence interval: 2.57-21.8]. Among lesions without prior SRS, higher volume of uninvolved brain receiving 25 Gy (BrainV25; HR: 1.07 [1.02-1.12]) and 30 Gy (BrainV30; HR: 1.07 [1.01-1.33]) were the most significant factors associated with sRN. Similar results were also observed among the patients with prior SRS. For lesions without prior SRS, BrainV25 > 16 cm³ (HR: 11.7 [1.47-93.3]) and BrainV30 > 10 cm³ (HR: 7.08 [1.52-33.0]) were associated with significantly higher risk of sRN. At two years, the sRN incidence was 21% if violating either dosimetric threshold and 2% if violating neither ($p = .007$). **CONCLUSION:** BrainV25 and BrainV30 are significant dosimetric predictors of sRN of brain metastases treated with 5fSRS. In the absence of prior SRS, maintaining BrainV25Gy < 16 cm³ and BrainV30Gy < 10 cm³ may minimize sRN risk.

[4] Gamma Knife Radiosurgery for Brain Metastases in Non-Small Cell Lung Cancer Patients Treated with Immunotherapy or Targeted Therapy.

Cancers (Basel). 2020 Dec 7;12(12). pii: cancers12123668. Cho A, Untersteiner H, Hirschmann D, Shaltout A, Gobl P, Dorfer C, Rossler K, Marik W, Kirchbacher K, Kapfhammer I, Zochbauer-Muller S, Gatterbauer B, Hochmair MJ, Frischer JM PMID: 33297416 DOI: 10.3390/cancers12123668

The combination of Gamma Knife radiosurgery (GKRS) and systemic immunotherapy (IT) or targeted therapy (TT) is a novel treatment method for brain metastases (BMs) in non-small cell lung cancer (NSCLC). To elucidate the safety and efficacy of concomitant IT or TT on the outcome after GKRS, 496 NSCLC patients with BMs, who were treated with GKRS were retrospectively reviewed. The median time between the initial lung cancer diagnosis and the diagnosis of brain metastases was one month. The survival after the initial BM diagnosis was significantly longer than the survival predicted by prognostic BM scores. After the first Gamma Knife radiosurgery treatment (GKRS1), the estimated median survival was 9.9 months (95% CI = 8.3-11.4). Patients with concurrent IT or TT presented with a significantly longer survival after GKRS1 than patients without IT or TT ($p < 0.001$). These significant differences in the survival were also apparent among the four treatment groups and remained significant after adjustment for

Karnofsky performance status scale (KPS), recursive partitioning analysis (RPA) class, sex, and multiple BMs. About half of all our patients (46%) developed new distant BMs after GKRS1. Of note, no statistically significant differences in the occurrence of radiation reaction, radiation necrosis, or intrasellar hemorrhage in association with IT or TT at or after GKRS1 were observed. In NSCLC-BM patients, the concomitant use of GKRS and IT or TT showed an increase in overall survival without increased complications related to GKRS. Therefore, the combined treatment with GKRS and IT or TT seems to be a safe and powerful treatment option and emphasizes the role of radiosurgery in modern BM treatment.

[5] Immune Checkpoint Inhibitors for Non-Small-Cell Lung Cancer with Brain Metastasis : The Role of Gamma Knife Radiosurgery.

J Korean Neurosurg Soc. 2020 Dec 4. pii: jkns.2020.0135.

Lee MH, Cho KR, Choi JW, Kong DS, Seol HJ, Nam DH, Jung HA, Sun JM, Lee SH, Ahn JS, Ahn MJ, Park K, Lee JI

PMID: 33267531 DOI: 10.3340/jkns.2020.0135

OBJECTIVE: Immune checkpoint inhibitors (ICIs) are approved for treating non-small-cell lung cancer (NSCLC); however, the safety and efficacy of combined ICI and Gamma Knife radiosurgery (GKS) treatment remain undefined. In this study, we retrospectively analyzed patients treated with ICIs with or without GKS at our institute to manage patients with brain metastases from NSCLC. **METHODS:** We retrospectively reviewed medical records of patients with brain metastases from NSCLC treated with ICIs between January 2015 and December 2017. Of 134 patients, 77 were assessable for brain responses and categorized into three groups as follows : group A, ICI alone (n=26); group B, ICI with concurrent GKS within 14 days (n=24); and group C, ICI with non-concurrent GKS (n=27). **RESULTS:** The median follow-up duration after brain metastasis diagnosis was 19.1 months (range, 1-77). At the last follow-up, 53 patients (68.8%) died, 20 were alive, and four were lost to follow-up. The estimated median overall survival (OS) of all patients from the date of brain metastasis diagnosis was 20.0 months (95% confidence interval, 12.5-27.7) (10.0, 22.5, and 42.1 months in groups A, B, and C, respectively). The OS was shorter in group A than in group C (p=0.001). The intracranial disease progression-free survival (p=0.569), local progression-free survival (p=0.457), and complication rates did not significantly differ among the groups. Twelve patients showed leptomeningeal seeding (LMS) during follow-up. The 1-year LMS-free rate in treated with ICI alone group (69.1%) was significantly lower than that in treated with GKS before ICI treatment or within 14 days group (93.2%) (p=0.004). **CONCLUSION:** GKS with ICI showed no favorable OS outcome in treating brain metastasis from NSCLC. However, GKS with ICI did not increase the risk of complications. Furthermore, compared with ICI alone, GKS with ICI may be associated with a reduced incidence of LMS. Further understanding of the mechanism, which remains unknown, may help improve the quality of life of patients with brain metastasis.

[6] Early magnetic resonance imaging after gamma knife radiosurgery of brain metastases.

World Neurosurg. 2020 Nov 27. pii: S1878-8750(20)32504-3.

Benveniste RJ, Yechieli R, Diwanji T

PMID: 33253947 DOI: 10.1016/j.wneu.2020.11.119

BACKGROUND: Gamma knife radiosurgery (GKRS) is commonly performed to treat brain metastases (BrM). Widely referenced guidelines suggest post treatment imaging at 3 month intervals, but clinicians frequently obtain earlier MRI. **METHODS:** We performed a retrospective chart review study in order to assess the utility of early (before 3 months) post GKRS MRI in patients with BrM. **RESULTS:** 415 GKRS procedures were performed. In 325 cases, early imaging was obtained. 31 patients had new or worsened neurological symptoms. Early MRI showed adverse findings in 25 (78%), and in 23 (72%), resulted in a change in treatment. In 294 cases, there were no new or worsened neurological symptoms at the time of the early MRI. Among these patients, 86 (29%) had at least one adverse finding on MRI, and 60 (20%) had a change in management as a result. However, there were no rapidly growing tumors or other emergent adverse

findings. **CONCLUSIONS:** Early post GKRS MRI (within 3 months after treatment) frequently shows adverse findings in even asymptomatic patients, more commonly in patients younger than 65 years and patients with multiple treated BrM. However, based on the nature of the adverse findings observed in our retrospective study, it is unlikely that clinical outcomes would have been affected if the post GKRS MRI had been deferred until 3 months after treatment. Our data support deferring post GK MRI to three months after treatment, in the absence of new neurological signs or symptoms.

[7] The Utilization of Treatment Response Assessment Maps in Discriminating Between Radiation Effect and Persistent Tumoral Lesion in Metastatic Brain Tumors Treated with Gamma Knife Radiosurgery.

World Neurosurg. 2020 Nov 27. pii: S1878-8750(20)32499-2.

Peker S, Samanci Y, Serhat Aygun M, Yavuz F, Emre Erden M, Emre Nokay A, Ihsan Atasoy A, Bolukbasi Y

PMID: 33253956 DOI: 10.1016/j.wneu.2020.11.114

BACKGROUND: Traditional imaging modalities are not useful in the follow-up of irradiated metastatic brain tumors (MBTs), as radiation can change imaging characteristics. We aimed to assess the ability of treatment response assessment maps (TRAMs) calculated from delayed-contrast MR images in differentiation between radiation effect and persistent tumoral tissue. **METHODS:** TRAMs were calculated by subtracting 3D-T1-MR images acquired 5 minutes after contrast injection from the images acquired 60-105 minutes later. Red areas were regarded as radiation effect and blue areas as persistent tumoral lesion. Thirty-seven patients with 130 MBTs who were treated with Gamma Knife radiosurgery, and who underwent TRAMs, perfusion MRI (PW) were enrolled in this retrospective study. **RESULTS:** Median age was 58 years and the most common primary diagnosis was lung cancer (n = 21). Median follow-up period of the subjects was 12 months. The overall local control rate was 100% at one year and 98.9% at two years. Median progression-free survival was 12 months. The mean overall survival was 27.3 months. The radiological and clinical follow-up revealed a clinico-radiological diagnosis of a persistent tumoral lesion in three tumors (2.3%) and radiation effect in 127 tumors (97.7%). There was a fair agreement between clinico-radiological diagnosis and TRAMs analysis (kappa = 0.380). The sensitivity and PPV of TRAMs in diagnosing radiation effect was 96.06% and 99.2%, respectively. TRAMs revealed comparable results to PW-MRI with a diagnostic odds ratio of 27.4 versus 20.7, respectively. **CONCLUSIONS:** The presented results demonstrate the ability of TRAMs in differentiating radiation effect and persistent tumoral lesions.

[8] A graded prognostic model for patients surviving 3 years or more (GPM>=3Ys) after stereotactic radiosurgery for brain metastasis.

Radiother Oncol. 2020 Nov 26. pii: S0167-8140(20)31194-4.

Sato Y, Yamamoto M, Serizawa T, Yamada KI, Higuchi Y, Kasuya H

PMID: 33249092 DOI: 10.1016/j.radonc.2020.11.024

BACKGROUND AND PURPOSE: As more cancer patients with brain metastases (BM) are surviving longer due to recent advancements in various treatment modalities, we developed a grading system for stereotactic radiosurgery (SRS)-treated BM patients with long survival. This is a Graded Prognostic Model for Patients Surviving 3 Years or More (GPM>=3Ys). **MATERIALS AND METHODS:** First, using clinical factor-survival time analysis of 3237 patients in whom gamma knife (GK) SRS was performed by the second author (test cohort), we developed the GPM>=3Ys based on survival >=3 years as the objective variable. The validity of this model was then tested using another series of 3317 patients independently undergoing GK SRS performed by the third author (verification cohort). Number of patients surviving 3 years or more were 289 (8.9%) and 348 (10.5%), respectively. **RESULTS:** Using the Y-series, among various pre-SRS clinical factors, noted below, five were shown to be highly correlated with survival of >=3 years. Therefore, we assigned scores for these five factors, i.e., "tumor numbers 1/2-4/>=5 (score; 6/1/0)", "female/male (5/0)", "KPS >=80%/<80% (5/0)", "primary cancers of breast/lung/gastrointestinal tract/other (score; 1/0/3/0)",

"controlled primary cancer/not (8/0)" and "existing extra-cerebral metastases/not (5/0). Patients were categorized into four grades according to the sum of scores, i.e., 0-9, 10-19, 20-29 and 30-36. Post-SRS mean survival times (MSTs) differed significantly ($p < 0.0001$) with no overlapping of 95% confidence intervals (CIs) among the four grades. Also, in the S-series, MSTs differed significantly ($p < 0.0001$) with no overlapping of 95% CI among the four grades of the GPM \geq 3Ys system. **CONCLUSION:** Although this was a retrospective study, the GPM \geq 3Ys system was shown to be very useful to physicians selecting among more aggressive treatment modalities for patients in whom longer survival can be expected.

[9] Pre-radiosurgery leucocyte ratios and modified glasgow prognostic score predict survival in non-small cell lung cancer brain metastases patients.

J Neurooncol. 2020 Nov 11. pii: 10.1007/s11060-020-03660-z.

Cho A, Untersteiner H, Hirschmann D, Fitschek F, Dorfer C, Rossler K, Zochbauer-Muller S, Gatterbauer B, Hochmair MJ, Frischer JM

PMID: 33179214 DOI: 10.1007/s11060-020-03660-z

INTRODUCTION: The predictive value of the pre-radiosurgery Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), Lymphocyte-to-Monocyte Ratio (LMR) and the modified Glasgow Prognostic Score (mGPS) was assessed for the first time in a homogenous group of NSCLC brain metastases (BM) patients. **METHODS:** We retrospectively evaluated 185 NSCLC-BM patients, who were treated with Gamma Knife Radiosurgery (GKRS). Patients with immunotherapy or targeted therapy were excluded. Routine laboratory parameters were reviewed within 14 days before GKRS1. **RESULTS:** Median survival after GKRS1 was significantly longer in patients with $NLR < 5$ ($p < 0.001$), $PLR < 180$ ($p = 0.003$) and $LMR \geq 4$ ($p = 0.023$). The Cox regression model for the continuous metric values revealed that each increase in the NLR of 1 equaled an increase of 4.3% in risk of death (HR: 1.043; 95%CI = 1.020-1.067, $p < 0.001$); each increase in the PLR of 10 caused an increase of 1.3% in risk of death (HR: 1.013; 95%CI = 1.004-1.021; $p = 0.003$) and each increase in the LMR of 1 equaled a decrease of 20.5% in risk of death (HR: 0.795; 95%CI = 0.697-0.907; $p = 0.001$). Moreover, the mGPS group was a highly significant predictor for survival after GKRS1 ($p < 0.001$) with a HR of 2.501 (95%CI = 1.582-3.954; $p < 0.001$). NLR, PLR, LMR values and mGPS groups were validated as independent prognostic factors for risk of death after adjusting for sex, KPS, age and presence of extracranial metastases. **CONCLUSION:** NLR, PLR, LMR and mGPS represent effective and simple tools to predict survival in NSCLC patients prior to radiosurgery for brain metastases.

[10] Health-related quality of life after Gamma Knife radiosurgery in patients with 1-10 brain metastases.

J Cancer Res Clin Oncol. 2020 Oct 6. pii: 10.1007/s00432-020-03400-w.

Verhaak E, Schimmel WCM, Gehring K, Emons WHM, Hanssens PEJ, Sitskooon MM

PMID: 33025282 DOI: 10.1007/s00432-020-03400-w

PURPOSE: Increasingly more patients with multiple (> 4) brain metastases (BM) are being treated with stereotactic radiosurgery (SRS). Preserving patients' health-related quality of life (HRQoL) is an important treatment goal. The aim of this study was to assess (individual) changes in HRQoL in patients with 1-10 BM over time. **METHODS:** A total of 92 patients were assessed before ($n = 92$) and at 3 ($n = 66$), 6 ($n = 53$), and 9 ($n = 41$) months after Gamma Knife radiosurgery (GKRS), using the Functional Assessment of Cancer Therapy-Brain (FACT-Br). The course of HRQoL was analyzed using linear mixed models. Clinical minimally important differences were used to evaluate individual changes. **RESULTS:** At group level, patients' physical well-being worsened, whereas emotional well-being improved over 9 months. Scores on other HRQoL subscales did not change significantly. Number (1-3 versus 4-10) and volume (small, medium, and large) of BM did not influence HRQoL over time, except for the subscale additional concerns; medium intracranial tumor volume was associated with less additional concerns. On the individual level as well, physical well-being declined while emotional well-being improved in most patients over 9 months after GKRS. At patient level, however,

most patients had both declines as well as improvements in the different HRQoL aspects. **CONCLUSION:** Our results indicate that even in patients with up to 10 BM, both at group and individual subscale level, aspects of HRQoL remained stable over nine months after GKRS, except for an improvement in emotional well-being and a decline in physical well-being. Nevertheless, HRQoL scores varied considerably at the individual patient level. TRAIL REGISTRATION NUMBER: ClinicalTrials.gov Identifier: NCT02953756, November 3, 2016.

[11] The Effect of Epidermal Growth Factor Receptor Mutation on Intracranial Progression-Free Survival of Non-Small Cell Lung Cancer Patients with Brain Metastasis Underwent Gamma Knife Radiosurgery.

Brain Tumor Res Treat. 2020 Oct;8(2):103-108.

Yang SH, Kim HY, Lee SI, Jin SJ

PMID: 33118342 DOI: 10.14791/btrt.2020.8.e15

BACKGROUND: The aim of this study was to survey prognostic factors, particularly those focusing on epidermal growth factor receptor (EGFR) mutations, of patients with non-small cell lung cancer (NSCLC) after Gamma Knife Radiosurgery (GKRS) for metastatic brain tumors. **METHODS:** We retrospectively reviewed the medical records of 98 patients with NSCLC who underwent GKRS for brain metastases from August 2010 to July 2017. The primary endpoint was progression-free survival (PFS) of the intracranial disease. We analyzed variables such as age, sex, Karnofsky Performance Status, recursive partitioning analysis (RPA) class, smoking status, primary cancer pathology, EGFR mutations, and time to brain metastases as prognostic factors. **RESULTS:** The median overall survival (OS) of the patients was 16 months [95% confidence interval (CI), 13-21 months]. Median systemic PFS and intracranial PFS were 9 months (95% CI, 8-11 months) and 11 months (95% CI, 7-14 months), respectively. Kaplan-Meier survival analysis revealed that the patients with EGFR mutations had longer intracranial PFS than those without EGFR mutation (median intracranial PFS: 19 vs. 10 months with $p = 0.01$) while they had no benefits in OS and systemic PFS. Furthermore, the patients harboring adenocarcinoma had longer OS ($p < 0.01$) and intracranial PFS ($p < 0.01$) and the patients with lower RPA class had longer OS ($p = 0.02$) and intracranial PFS ($p = 0.03$). **CONCLUSION:** EGFR mutations, primary cancer pathology, and RPA class may be proposed as prognostic factors for intracranial PFS in NSCLC patients after GKRS for brain metastasis in this study.

[12] Radiosurgery for small-cell lung cancer brain metastases: a review.

J Thorac Dis. 2020 Oct;12(10):6234-6239.

Robin TP, Rusthoven CG

PMID: 33209462 DOI: 10.21037/jtd.2020.03.90

First-line stereotactic radiosurgery (SRS) is now considered the preferred treatment over whole brain radiation therapy (WBRT) for limited brain metastases arising from most tumor histologies. This standard was reached following the consistent results of multiple phase III studies which demonstrated that, despite improved CNS control, the addition of WBRT to SRS does not improve overall survival (OS) and is associated with a reduction in cognitive function. Thus, it may be reasonable to consider the benchmark necessary to favor a paradigm of SRS alone over strategies incorporating WBRT as the demonstration of comparable OS in the context of decreased treatment-related side effects. However, patients with small-cell lung cancer (SCLC) brain metastases were excluded from the landmark trials that established SRS alone for limited brain metastases, largely due to concerns for short-interval CNS progression in SCLC as well the historic role of prophylactic cranial irradiation (PCI) in SCLC in the absence of known brain metastases. As a result, WBRT has remained the standard for SCLC for limited and even solitary brain lesions. With shifting SCLC care patterns including increased MRI surveillance, decreased PCI delivery, and emerging systemic agents, interest in first-line SRS for SCLC is likely to continue to increase over time. Herein we will review the emerging data for first-line SRS in the management of SCLC brain metastases and the potential for its increasing role in the setting of a greater utilization of MRI surveillance and improving systemic therapies.

[13] Impact of Systemic Therapy Type and Timing on Intracranial Tumor Control in Patients with Brain Metastasis from Non-Small Cell Lung Cancer Treated With Stereotactic Radiosurgery.

World Neurosurg. 2020 Sep 18. pii: S1878-8750(20)32090-8.
Singh SA, McDermott DM, Mattes MD
PMID: 32956881 DOI: 10.1016/j.wneu.2020.09.082

OBJECTIVE: Stereotactic radiosurgery (SRS) can effectively control brain metastasis (BRM) from non-small cell lung cancer (NSCLC), though intracranial recurrence from untreated micrometastatic tumor deposits is common without whole brain radiotherapy (WBRT). Our goal was to determine if immunotherapy improves distant intracranial progression-free survival (DI-PFS) compared to other systemic therapies in patients treated with SRS. **METHODS:** All patients from 2011-2019 treated with SRS without prior WBRT for NSCLC BRM were reviewed. DI-PFS for the entire cohort, and subgroups of patients, was estimated and compared using the Kaplan-Meier/log rank method. **RESULTS:** One hundred and thirty-six SRS sessions used to treat 99 patients were reviewed; 98 (72%) for previously untreated BRM and 38 (28%) for recurrent BRM. 35% received immunotherapy (77% concurrent with SRS), 46% received chemotherapy (75% concurrent), and 18% received EGFR/ALK targeted therapy (85% concurrent). At median follow-up of 13.7 months, 49% developed distant intracranial recurrence. 1-year DI-PFS was improved with any use of immunotherapy (58% vs. 39%, $p=0.03$), and concurrent immunotherapy vs. chemotherapy or targeted therapy (67% vs. 37% vs. 39%, respectively, $p=0.01$). In the immunotherapy cohort, 1-year DI-PFS was improved for PD-L1 expression > 50% vs. 1-49% vs. 0% (80% vs. 49% vs. 19%, respectively, $p<0.01$), and Lung Immune Prognostic Index (LIPI) score 0-1 vs. 2 (63% vs. 34%, $p=0.03$). **CONCLUSIONS:** Immunotherapy concurrent with SRS, particularly in patients with high PD-L1 expression or low LIPI score, is associated with improved DI-PFS and no increased risk of radiation necrosis compared to other systemic therapies for NSCLC.

[14] Role of Gamma Knife Radiosurgery in Small Cell Lung Cancer: A Multi-Institutional Retrospective Study of the International Radiosurgery Research Foundation (IRRF).

Neurosurgery. 2020 Sep 15;87(4):664-671.
Cifarelli CP, Vargo JA, Fang W, Liscak R, Guseynova K, Warnick RE, Lee CC, Yang HC, Borghei-Razavi H, Maiti T, Siddiqui ZA, Yuan JC, Grills IS, Mathieu D, Touchette CJ, Cordeiro D, Chiang V, Hess J, Tien CJ, Faramand A, Kano H, Barnett GH, Sheehan JP, Lunsford LD
PMID: 31599324 DOI: 10.1093/neuros/nyz428

BACKGROUND: Despite a high incidence of brain metastases in patients with small-cell lung cancer (SCLC), limited data exist on the use of stereotactic radiosurgery (SRS), specifically Gamma Knife radiosurgery (Elekta AB), for SCLC brain metastases. **OBJECTIVE:** To provide a detailed analysis of SCLC patients treated with SRS, focusing on local failure, distant brain failure, and overall survival (OS). **METHODS:** A multi-institutional retrospective review was performed on 293 patients undergoing SRS for SCLC brain metastases at 10 medical centers from 1991 to 2017. Data collection was performed according to individual institutional review boards, and analyses were performed using binary logistic regression, Cox-proportional hazard models, Kaplan-Meier survival analysis, and competing risks analysis. **RESULTS:** Two hundred thirty-two (79%) patients received SRS as salvage following prior whole-brain irradiation (WBRT) or prophylactic cranial irradiation, with a median marginal dose of 18 Gy. At median follow-up after SRS of 6.4 and 18.0 mo for surviving patients, the 1-yr local failure, distant brain failure, and OS were 31%, 49%, and 28%. The interval between WBRT and SRS was predictive of improved OS for patients receiving SRS more than 1 yr after initial treatment (21%, <1 yr vs 36%, >1 yr, $P = .01$). On multivariate analysis, older age was the only significant predictor for OS (hazard ratio 1.63, 95% CI 1.16-2.29, $P = .005$). **CONCLUSION:** SRS plays an important role in the management of brain metastases from SCLC, especially in salvage therapy following WBRT. Ongoing prospective trials will better assess the value of radiosurgery in the primary management of SCLC brain metastases and potentially challenge the standard application of WBRT in SCLC patients.

[15] Prognostic value of pretreatment MRI texture features in breast cancer brain metastasis treated with Gamma Knife radiosurgery.

Acta Radiol. 2020 Sep 10:284185120956296.
Zheng Y, Geng D, Yu T, Xia W, She D, Liu L, Yin B
PMID: 32910684 DOI: 10.1177/0284185120956296

BACKGROUND: Gamma Knife radiosurgery (GKS) was recommended for treating patients with breast cancer brain metastasis (BCBM), but predictions of the existing prognostic models for therapeutic responsiveness vary substantially. **PURPOSE:** To investigate the prognostic value of pretreatment clinical, MRI radiologic, and texture features in patients with BCBM undergoing GKS. **MATERIAL AND METHODS:** The data of 81 BCBMs in 44 patients were retrospectively reviewed. Progressive disease was defined as an increase of at least 20% in the longest diameter of the target lesion or the presence of new intracranial lesions on contrast-enhanced T1-weighted (CE-T1W) imaging. Radiomic features were extracted from pretreatment CE-T1W images, T2-weighted (T2W) images, and ADC maps. Cox proportional hazard analyses were performed to identify independent predictors associated with BCBM-specific progression-free survival (PFS). A nomogram was constructed and its calibration ability was assessed. **RESULTS:** The cumulative BCBM-specific PFS was 52.27% at six months and 11.36% at one year, respectively. Age (hazard ratio [HR] 1.04; 95% confidence interval [CI] 1.01-1.06; $P = 0.004$) and CE-T1W-based kurtosis (HR 0.72; 95% CI 0.57-0.92; $P = 0.008$) were the independent predictors. The combination of CE-T1W-based kurtosis and age displayed a higher C-index (C-index 0.70; 95% CI 0.63-0.77) than did CE-T1W-based kurtosis (C-index 0.65; 95% CI 0.57-0.73) or age (C-index 0.63; 95% CI 0.56-0.70) alone. The nomogram based on the combinative model provided a better performance over age ($P < 0.05$). The calibration curves elucidated good agreement between prediction and observation for the probability of 7- and 12-month BCBM-specific PFS. **CONCLUSION:** Pretreatment CE-T1W-based kurtosis combined with age could improve prognostic ability in patients with BCBM undergoing GKS.

[16] Metastatic renal cell carcinoma to the brain: optimizing patient selection for gamma knife radiosurgery.

Acta Neurochir (Wien). 2020 Sep 9. pii: 10.1007/s00701-020-04537-w.
Stenman M, Benmakhlof H, Wersall P, Johnstone P, Hatiboglu MA, Mayer-da-Silva J, Harmenberg U, Lindskog M, Sinclair G
PMID: 32902689 DOI: 10.1007/s00701-020-04537-w

INTRODUCTION: The effects of single-fraction gamma knife radiosurgery (sf-GKRS) on patients with renal cell carcinoma (RCC) brain metastases (BM) in the era of targeted agents (TA) and immune checkpoint inhibitors (ICI) are insufficiently studied. **METHODS AND MATERIALS:** Clear cell metastatic RCC patients treated with sf-GKRS due to BM in 2005-2014 at three European centres were retrospectively analysed ($n = 43$). Median follow-up was 56 months. Ninety-five percent had prior nephrectomy, 53% synchronous metastasis and 86% extracranial disease at first sf-GKRS. Karnofsky performance status (KPS) ranged from 60 to 100%. Outcome measures were overall survival (OS), local control (LC) and adverse radiation effects (ARE). **RESULTS:** One hundred and ninety-four targets were irradiated. The median number of targets at first sf-GKRS was two. The median prescription dose was 22.0 Gy. Thirty-seven percent had repeated sf-GKRS. Eighty-eight percent received TA. LC rates at 12 and 18 months were 97% and 90%. Median OS from the first sf-GKRS was 15.7 months. Low serum albumin (HR for death 5.3), corticosteroid use pre-sf-GKRS (HR for death 5.8) and KPS < 80 (HR for death 9.1) were independently associated with worse OS. No further prognostic information was gleaned from MSKCC risk group, synchronous metastasis, age, number of BM or extracranial metastases. Other prognostic scores for BM radiosurgery, including DS-GPA, renal-GPA, LLV-SIR and CITV-SIR, again, did not add further prognostic value. ARE were seldom symptomatic and were associated with tumour volume, 10-Gy volume and pre-treatment perifocal oedema. ARE were less common among patients treated with TA within 1 month of sf-GKRS. **CONCLUSIONS:** We identified albumin, corticosteroid use and KPS as independent prognostic factors for sf-GKRS of clear cell RCC BM. Studies

focusing on the prognostic significance of albumin in sf-GKRS are rare. Further studies with a larger number of patients are warranted to confirm the above analytical outcome. Also, in keeping with previous studies, our data showed optimal rates of local tumour control and limited toxicity post radiosurgery, rendering GKRS the tool of choice in the management of RCC BM.

[17] Stereotactic radiosurgery for brain metastases: A retrospective cohort study comparing treatment results between two lung cancer patient age groups, 75 years or older vs 65-74 years.

Lung Cancer. 2020 Aug 18;149:103-112.

Yamamoto M, Serizawa T, Sato Y, Higuchi Y, Kasuya H, Barfod BE

PMID: 33007676 DOI: 10.1016/j.lungcan.2020.07.037

BACKGROUND: There is little information on stereotactic radiosurgery (SRS) results for brain metastases (BMs) in lung cancer patients ≥ 75 years of age. We aimed to reappraise whether SRS results for patients ≥ 75 (very elderly) differ from those of patients with 65-74 years old (elderly). **METHODS:** This IRB-approved retrospective cohort study was based on our prospectively-accumulated database including 7351 consecutive patients undergoing gamma knife (GK) SRS performed for BMs by two highly experienced neurosurgeons during the 1998-2018 period. We selected a total of 2915 elderly patients (age ≥ 65 years, 39.7 % of the 7351) with lung cancers (902 females, 2013 males, median age; 72 [maximum; 96] years, 2441 NSCLCs, 474 SCLCs) for this study. **RESULTS:** Post-SRS median survival times (MSTs, months) differed significantly between the two lung cancer types, NSCLC (9.0) and SCLC (7.2, $p < 0.0001$). In NSCLC patients, post-SRS MSTs were significantly shorter in the very elderly (9.7) than those in the elderly (7.8) group ($p < 0.0001$). However, in SCLC patients, there were no significant MST differences (7.3 vs 6.9, $p = 0.52$) between the two age groups. In both NSCLC and SCLC patients, neither crude nor cumulative incidences of secondary endpoints in the very elderly group, i.e., neurological death, neurological deterioration, local recurrence, repeat SRS, salvage whole brain radiotherapy and SRS-related complications, were shown to be unfavorable to those in the elderly group. **CONCLUSIONS:** Our results suggest that carefully-selected patients ≥ 75 years of age are not poor candidates for SRS as compared to those 65-74 years old.

[18] Cumulative intracranial tumour volume prognostic assessment: a new predicting score index for patients with brain metastases treated by stereotactic radiosurgery.

Clin Exp Metastasis. 2020 Aug;37(4):499-508.

Donofrio CA, Cavalli A, Gemma M, Riccio L, Donofrio A, Panni P, Ferrari da

Passano C, Del Vecchio A, Bolognesi A, Soffietti R, Mortini P

PMID: 32430649 DOI: 10.1007/s10585-020-10037-z

Brain metastases (BM) represent the most common intracranial malignancy in adults. Limitations of existing prognostic models reduce their predictivity and clinical applicability. The aim of this study is to validate the cumulative intracranial tumour volume prognostic assessment (CITVPA) as a new prognostic score system for patients with BM treated by Stereotactic Radiosurgery (SRS). Between January 2001 and December 2015, 1894 patients underwent Gamma Knife SRS treatment. The CITVPA model was implemented and validated as follows: the CITV cut-offs were identified thanks to a receiver-operating characteristic (ROC) curve analysis; the survival predictive factors were selected through a Cox proportional hazard model; its prognostic power was compared to RPA, SIR and GPA through the Harrel concordance index (HCI). According to the ROC curve analysis, the CITV cut-off values were set at 1.5 and 4.0 cc. Based on the multivariate analysis, the CITVPA model included: age (OR 1.010, 95% CI 1.005-1.015, $p < 0.001$), KPS (OR 0.960, 95% CI 0.956-0.965, $p < 0.001$), extracranial metastases (OR 1.287, 95% CI 1.154-1.437, $p < 0.001$), BM number (OR 1.193, 95% CI 1.047-1.360, $p = 0.008$), and CITV (OR 1.028, 95% CI 1.020-1.036, $p < 0.001$). A score between 0 and 1 was attributed to each prognosticator; a global CITVPA score ranging from 0 to 5 was assigned with higher results corresponding to worse outcomes. The CITVPA (HCI = 0.64) exhibited a significantly ($p < 0.001$) higher prognostic power compared to

RPA (HCI = 0.55), SIR (HCI = 0.55) and GPA (HCI = 0.61). The CITVPA represents a reliable prognostic system for patients with BM treated by SRS. However, further prospective and multicentric studies are necessary before its applicability in clinical practice.

[19] Gamma Knife Surgery for Brain Metastases from Uterine Malignant Tumor.

World Neurosurg. 2020 Jul;139:e363-e372.

Ogino A, Hirai T, Serizawa T, Yoshino A

PMID: 32305598 DOI: 10.1016/j.wneu.2020.03.225

BACKGROUND: Uterine malignant tumors (uterine cervical carcinoma [UCC], uterine endometrial carcinoma, and uterine sarcoma) are common in women. Brain metastases from uterine malignant tumors are rare, but its incidence has been increasing. The present study aimed to investigate the characteristics of brain metastases from uterine malignant tumors, evaluate predictive factors, and assess the efficacy of Gamma Knife surgery (GKS) for metastases from uterine malignant tumors. **METHODS:** We retrospectively reviewed the records of patients with brain metastases from uterine malignant tumors treated at Tokyo Gamma Unit Center from 2005 to 2017. **RESULTS:** We identified 37 patients: 16 had UCC, 12 had uterine endometrial carcinoma, and 9 had uterine sarcoma. Their median age at diagnosis of brain metastases was 54.0 years. The median interval from diagnosis of uterine malignant tumor to brain metastases was 21.0 months, the median number of brain metastases was 3.0, and the median Karnofsky Performance Status at first GKS was 80%. The median survival after first GKS was 6.0 months. All patients had other metastases. Six-month and 1-year survival after first GKS were 48.9% and 32.6%, respectively, and the tumor control rate at 6 months after GKS was 90.8%. Brain metastases from UCC were significantly correlated with good tumor control ($P = 0.024$). Multivariate analysis determined that Karnofsky Performance Status was significantly associated with patient survival ($P = 0.001$). **CONCLUSIONS:** The results of our study suggest that GKS is an acceptable choice for controlling brain metastases from uterine malignant tumors. In particular, GKS provides excellent local control for metastases from UCC.

[20] Identification and Management of Progressive Enhancement After Radiation Therapy for Brain Metastases: Results from a Neurosurgical Survey.

World Neurosurg. 2020 Jul;139:e526-e540.

Semonche A, Patel NV, Yang I, Danish SF

PMID: 32311550 DOI: 10.1016/j.wneu.2020.04.046

OBJECTIVE: There is a lack of consensus regarding diagnosis, timing, and method of intervention for progressive enhancement on surveillance imaging after stereotactic radiosurgery (SRS) treatment of brain metastases. We sought to characterize current practices among neurosurgeons in identifying and treating infield tumor recurrence (TR) or radiation necrosis (RN) after SRS for brain metastases. **METHODS:** A voluntary survey was distributed electronically to preidentified neurosurgeons. Results were analyzed using descriptive statistics and chi(2) analysis. **RESULTS:** A total of 120 participants completed the survey from 72 U.S. and 17 international centers. Most (69.2%) agreed that growth over ≥ 2 surveillance scans spaced ≥ 90 days apart identified irreversible progression after SRS for brain metastases. Respondents were evenly divided on the need for tissue biopsy to distinguish between TR and RN. Preferred treatment modality and time frame to initiate treatment of suspected RN differed among neurosurgeons based on SRS case volume for brain metastases ($P = 0.002$ and $P = 0.02$, respectively). Neurosurgeons who used magnetic resonance-guided laser interstitial thermal therapy (LITT) for brain metastases were more likely to prefer LITT for suspected RN, whereas those with minimal LITT experience preferred steroids ($P < 0.0001$). Neurosurgeons in the United States were more likely to prefer LITT for RN (37.3%) compared with international counterparts (0%). **CONCLUSIONS:** Our survey of practicing neurosurgeons highlights areas of controversy in distinguishing between TR and RN and preferred management of suspected RN.

[21] Predicting the Local Response of Metastatic Brain Tumor to Gamma Knife Radiosurgery by Radiomics With a Machine Learning Method.

Front Oncol. 2021 Jan 11;10:569461.

Kawahara D, Tang X, Lee CK, Nagata Y, Watanabe Y
PMID: 33505904 DOI: 10.3389/fonc.2020.569461

PURPOSE: The current study proposed a model to predict the response of brain metastases (BMs) treated by Gamma knife radiosurgery (GKRS) using a machine learning (ML) method with radiomics features. The model can be used as a decision tool by clinicians for the most desirable treatment outcome. **METHODS AND MATERIAL:** Using MR image data taken by a FLASH (3D fast, low-angle shot) scanning protocol with gadolinium (Gd) contrast-enhanced T1-weighting, the local response (LR) of 157 metastatic brain tumors was categorized into two groups (Group I: responder and Group II: non-responder). We performed a radiomics analysis of those tumors, resulting in more than 700 features. To build a machine learning model, first, we used the least absolute shrinkage and selection operator (LASSO) regression to reduce the number of radiomics features to the minimum number of features useful for the prediction. Then, a prediction model was constructed by using a neural network (NN) classifier with 10 hidden layers and rectified linear unit activation. The training model was evaluated with five-fold cross-validation. For the final evaluation, the NN model was applied to a set of data not used for model creation. The accuracy and sensitivity and the area under the receiver operating characteristic curve (AUC) of the prediction model of LR were analyzed. The performance of the ML model was compared with a visual evaluation method, for which the LR of tumors was predicted by examining the image enhancement pattern of the tumor on MR images. **RESULTS:** By the LASSO analysis of the training data, we found seven radiomics features useful for the classification. The accuracy and sensitivity of the visual evaluation method were 44 and 54%. On the other hand, the accuracy and sensitivity of the proposed NN model were 78 and 87%, and the AUC was 0.87. **CONCLUSIONS:** The proposed NN model using the radiomics features can help physicians to gain a more realistic expectation of the treatment outcome than the traditional method.

[22] Treating Brain Metastases from Breast Cancer: Outcomes after Stereotactic Radiosurgery.

Clin Oncol (R Coll Radiol). 2020 Jun;32(6):390-396.

Wilson TG, Robinson T, MacFarlane C, Spencer T, Herbert C, Wade L, Reed H, Braybrooke JP

PMID: 32131980 DOI: 10.1016/j.clon.2020.02.007

AIMS: Stereotactic radiosurgery (SRS) is an alternative to surgery or whole brain radiotherapy for the control of single or multiple brain metastases in patients with breast cancer. To date, there is no clear consensus on factors that might predict overall survival following SRS. The aim of this study was to assess the overall survival of breast cancer patients with brain metastases treated with SRS at a single centre and to examine the factors that might influence survival. **MATERIALS AND METHODS:** A retrospective analysis of consecutive patients with breast cancer and brain metastases, considered suitable for SRS by the regional neuro-oncology multidisciplinary team. All patients were treated at a single National Health Service centre. **RESULTS:** In total, 91 patients received SRS between 2013 and 2017, of whom 15 (16.5%) were alive at the time of analysis. The median overall survival post-SRS was 15.7 months (interquartile range 7.7-23.8 months) with no significant effect of age on survival (67 patients \leq 65 years, 16.3 months; 26 patients $>$ 65 years, 11.4 months, $P = 0.129$). The primary tumour receptor status was an important determinant of outcome: 31 oestrogen receptor positive (ER+)/human epidermal growth factor receptor 2 negative (HER2-) patients had a median overall survival of 13.8 months, 14 ER+/HER2+ patients had a median overall survival of 21.4 months, 30 ER-/HER2+ patients had a median overall survival of 20.4 months and 16 patients with triple negative breast cancer (TNBC) had a median overall survival of 8.5 months. A larger total volume of tumour treated (>10 cm³), but not the number of individual metastases treated, was associated with worse survival ($P = 0.0002$) in this series. Patients with stable extracranial disease at the time of SRS had improved overall survival compared

with those with progressive extracranial disease (30 patients stable extracranial disease overall survival = 20.1 months versus 33 patients progressive extracranial disease overall survival = 11.4 months; $P = 0.0011$). Seventeen patients had no extracranial disease at the time of SRS, with a median overall survival of 13.1 months. **CONCLUSIONS:** This single-centre series of consecutive patients with brain metastases from breast cancer, treated with SRS, had a similar overall survival compared with previous studies of SRS. TNBC and ER+/HER2- histology, metastatic volumes >10 cm³ and progressive extracranial disease at the time of SRS were associated with worse survival.

[23] Pre-stereotactic radiosurgery neutrophil-to-lymphocyte ratio is a predictor of the prognosis for brain metastases.

J Neurooncol. 2020 May;147(3):691-700.

Zhang L, Hu Y, Chen W, Tian Y, Xie Y, Chen J

PMID: 32253715 DOI: 10.1007/s11060-020-03477-w

PURPOSE: The neutrophil-to-lymphocyte ratio (NLR) has been reported to relate to the prognosis of various cancers. The aim of this study was to elucidate the efficiency of pre-treatment NLR as a predictor of outcomes of brain metastasis underwent gamma knife radiosurgery (GKRS). **METHODS:** We analyzed 195 cases with brain metastasis underwent GKRS at our institution between January 2015 and April 2018. Patients' clinical and radiographic data were collected. **RESULTS:** We identified 458 brain metastases in 195 patients. Optimal dichotomous cutoff values of NLR determined by receiver operating characteristic analysis for local control, distant control and overall survival (OS) were 2.48, 2.74 and 3.13, respectively. The actuarial local control rates of patients with high NLR were 87.4% at 6 months and 76.1% at 12 months, whereas that of patients with low NLR were 94.2% at 6 months and 88.3% at 12 months ($P = 0.001$). The actuarial distant control rates of patients with high NLR were 31.4% at 6 months and 18.9% at 12 months, whereas that of patients with low NLR were 58.5% at 6 months and 31.3% at 12 months ($P = 0.001$). The median OS of patients with high and low NLR were 10.0 months and 14.5 months, respectively ($P = 0.001$). Multivariate analysis demonstrates that high NLR independently predicts local failure (hazard ratio [HR], 2.281; $P = 0.003$), distant brain failure (HR 1.775; $P = 0.002$) and poorer overall survival (HR 1.494; $P = 0.034$). **CONCLUSION:** The pre-SRS NLR, a systemic inflammatory marker for treatment response, inversely predicts local control, distant control and OS in patients with brain metastasis.

[24] Temporal Change in Tumor Volume Following Stereotactic Radiosurgery to a Single Brain Metastasis.

World neurosurgery. 2020;136:e328-e333

Goethe EA, Rao G, Harvey A, Mesfin FB, Li M, Mahajan A, Ye J, Suki D

PMID: 31917308 DOI: 10.1016/j.wneu.2019.12.168

BACKGROUND: Stereotactic radiosurgery (SRS) can be used to achieve local control of metastatic brain lesions. However, the temporal response of these lesions to SRS is incompletely understood and quantified. We aimed to examine the temporal response to SRS of single brain metastases from 4 different primary cancers.

METHODS: A retrospective chart review was performed of patients who underwent SRS at our institution from 2009 to 2012. Clinical, treatment, and volumetric data were collected. All patients were treated according to Radiation Therapy Oncology Group 90-05 schema. **RESULTS:** This study included 204 patients (116 men and 88 women) with a median age of 61 years (range, 27-86 years). Of patients, 20 (10%) had breast cancer, 79 (39%) had non-small cell lung cancer, 69 (34%) had melanoma, and 36 (17%) had renal cell carcinoma. Initial overall median tumor volume was 0.8 cm³ (range, 0.02-16.9 cm³). Median tumor volume was 0.5 cm³ (range, 0.02-20.4 cm³) at 1 month after SRS, 0.3 cm³ (range, 0.02-10.8 cm³) at 3 months after SRS, and 0.4 cm³ (range, 0.02-18.6 cm³) at 6 months after SRS. Based on the joint model constructed from our results, we demonstrate a median 16% (95% confidence interval, 11%-20%) reduction in tumor volume every 30 days. **CONCLUSIONS:** The results of this study demonstrate a consistent reduction in tumor volume following SRS over a 6-month period. Responses were modest over the first 30 days but accelerated at 3 months and varied by tumor type.

[25] Whole brain radiation therapy plus focal boost may be a suitable strategy for brain metastases in SCLC patients: a multi-center study.

Radiat Oncol. 2020 Mar 25;15(1):70.

Ni M, Jiang A, Liu W, Sheng Y, Zeng H, Liu N, Gao Q, Wang Y, Yu J, Yuan S
PMID: 32213185 DOI: 10.1186/s13014-020-01509-3

BACKGROUND: The treatment for brain metastases in small cell lung cancer (SCLC) is still controversial. The purpose of this study was to compare different brain radiotherapy treatments on SCLC patients with brain metastases.

METHODS: In this multi-center retrospective study, SCLC patients who had undergone whole brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS) for brain metastases from January 2012 to December 2018 were retrospectively screened. **RESULTS:** A total of 263 eligible SCLC patients were included in this study, among whom, 73 were women and 190 were men. According to accepted brain radiotherapy, the remaining patients were divided into WBRT plus focal radiation boost (WBRT+boost), WBRT, and SRS groups. In pairwise comparisons of the overall survival (OS), WBRT+boost group led to longer survival than did WBRT both in all patients (17.9 vs 8.7 months; $P < 0.001$) and 140 matched patients (17.9 vs 11.7 months; $P = 0.045$). There were no significant differences in OS between WBRT+boost and SRS groups in all patients (17.9 vs 14.5 months; $P = 0.432$). Among 74 matched patients between WBRT+boost and SRS groups, however, patients who received WBRT+boost led to a longer survival than did SRS alone (21.8 vs 12.9 months; $P = 0.040$). In pairwise comparison of the intracranial progression-free survival time (iPFS), WBRT+boost group also showed survival advantages over WBRT (10.8 vs 6.5 months; $P = 0.005$) and SRS groups (10.8 vs 7.5 months; $P = 0.032$). **CONCLUSION:** Due to the SCLC-derived multiple brain metastases and better survival time, focal radiation boost combined with adjuvant WBRT may be a preferred strategy for SCLC patients with brain metastases.

[26] Adverse Radiation Effect After Hypofractionated Stereotactic Radiosurgery in 5 Daily Fractions for Surgical Cavities and Intact Brain Metastases.

International journal of radiation oncology, biology, physics. 2020;106(4):772-779

Faruqi S, Ruschin M, Soliman H, Myrehaug S, Zeng KL, Husain Z, Atenafu E, Tseng CL, Das S, Perry J, Maralani P, Heyn C, Mainprize T, Sahgal A
PMID: 31928848 DOI: 10.1016/j.ijrobp.2019.12.002

PURPOSE: Limited data exist quantifying the risk of adverse radiation effect (ARE) specific to hypofractionated stereotactic radiosurgery (HSRS). We present our analyses of the risk of ARE after 5 daily fractions of HSRS to surgical cavities and intact metastases. **METHODS AND MATERIALS:** One hundred and eighty-seven consecutively treated patients with 118 surgical cavities and 132 intact metastases were retrospectively reviewed. All patients were treated with 5 daily fractions with a 2 mm planning target volume applied. Clinical and dosimetric variables were assessed to identify predictors of ARE. **RESULTS:** The median total prescribed dose was 30 Gy (range, 20-35 Gy) and median follow-up was 12 months. One hundred forty-four patients (77%) received treatment to a single target. Median planning target volumes for resection cavity and intact metastases were 24.9 cm³ and 7.7 cm³, respectively. ARE and symptomatic ARE were observed 21.2% and 10.8% of targets, respectively, and the median time to ARE was 8 months. Time to ARE was <6 months for 38%, 6 to 12 months for 43%, and >12 months for 19% of targets. Multivariable analysis identified intact metastases versus cavities (odds ratio [OR], 3.65; 95% confidence interval [CI], 1.33-10) as a significant predictor of symptomatic ARE. Specific to cavity HSRS, prior whole brain radiation therapy (OR 7.73; 95% CI, 1.67-35.69) and prior stereotactic radiosurgery (OR 8.66; 95% CI, 1.14-65.7) were significant predictors of symptomatic ARE. For intact metastases, the total brain minus gross tumor volume (GTV) receiving 30 Gy (BMC30) was a significant predictor of symptomatic ARE (OR, 1.21; 95% CI, 1.02-1.43), and a volume-based BMC30 threshold of 10.5 cm³ was significant with an OR of 7.21 (95% CI, 1.31-39.45). **CONCLUSIONS:** The risk of ARE was greater for intact metastases compared with cavities after HSRS. For intact lesions, the BMC30 was predictive for symptomatic necrosis, and a threshold of 10.5 cm³ may guide treatment planning.

[27] Comparison of two-stage Gamma Knife radiosurgery outcomes for large brain metastases among primary cancers.

Journal of neuro-oncology. 2020;147(1):237-246

Ito D, Aoyagi K, Nagano O, Serizawa T, Iwadate Y, Higuchi Y
PMID: 32026433 DOI: 10.1007/s11060-020-03421-y

PURPOSE: Stereotactic radiosurgery (SRS) is typically considered for patients who cannot undergo surgical resection for large (> 10 cm³) brain metastases (BMs). Staged SRS requires adaptive planning during each stage of the irradiation period for improved tumor control and reduced radiation damage. However, there has been no study on the tumor reduction rates of this method. We evaluated the outcomes of two-stage SRS across multiple primary cancer types. **METHODS:** We analyzed 178 patients with 182 large BMs initially treated with two-stage SRS. The primary cancers included breast (BC), non-small cell lung (NSCLC), and gastrointestinal tract cancers (GIC). We analyzed the overall survival (OS), neurological death, systemic death (SD), tumor progression (TP), tumor recurrence (TR), radiation necrosis (RN), and the tumor reduction rate during both stages. **RESULTS:** The median survival time after the first Gamma Knife surgery (GKS) procedure was 6.6 months. Compared with patients with BC and NSCLC, patients with GIC had shorter OS and a higher incidence of SD. Compared with patients with NSCLC and GIC, patients with BC had significantly higher tumor reduction rates in both sessions. TP rates were similar among primary cancer types. There was no association of the tumor reduction rate with tumor control. The overall cumulative incidence of RN was 4.2%; further, the RN rates were similar among primary cancer types. **CONCLUSIONS:** Two-stage SRS should be considered for BC and NSCLC if surgical resection is not indicated. For BMs from GIC, staged SRS should be carefully considered and adapted to each unique case given its lower tumor reduction rate and shorter OS.

[28] Three-institution study on applicability of initial brain metastasis velocity for breast cancer brain metastasis patients undergoing stereotactic radiosurgery.

Journal of neuro-oncology. 2020;147(1):177-184

Yamamoto M, Serizawa T, Nagano O, Aoyagi K, Higuchi Y, Sato Y, Kasuya H, Barford BE

PMID: 31989488 DOI: 10.1007/s11060-020-03412-z

PURPOSE: This study aimed to validate whether the recently-proposed prognostic grading system, initial brain metastasis velocity (iBMV), is applicable to breast cancer patients receiving stereotactic radiosurgery (SRS). We focused particularly on whether this grading system is useful for patients with all molecular types, i.e., positive versus negative for EsR, PgR and HER2. **METHODS AND MATERIALS:** This was an institutional review board-approved, retrospective cohort study using our database, prospectively accumulated at three gamma knife institutes, during the 20-year-period since 1998. We excluded patients for whom the day of primary cancer diagnosis was not available, had synchronous presentation, lacked information regarding molecular types, and/or had received pre-SRS radiotherapy and/or surgery. We ultimately studied 511 patients categorized into two classes by iBMV scores, i.e., < 2.00 and ≥ 2.00 . **RESULTS:** The median iBMV score for the entire cohort was 0.97 (IQR 0.39-2.84). Median survival time (MST) in patients with iBMV < 2.00, 15.9 (95% CI 13.0-18.6, IQR 7.5-35.5) months, was significantly longer than that in patients with iBMV ≥ 2.00 , 8.2 (95% CI 6.8-9.9, IQR 3.9-19.4) months (HR 1.582, 95% CI: 1.308-1.915, $p < 0.0001$). The same results were obtained in patients with EsR (-), PgR (-), HER2 (+) and HER2 (-) cancers, while MSTs did not differ significantly between iBMV < 2.00 vs ≥ 2.00 in patients with EsR (+) and PgR (+) cancers. **CONCLUSIONS:** This system was clearly shown to be applicable to breast cancer patients with SRS-treated BMs. However, this system is not applicable to patients with hormone receptor (+) breast cancer.

[29] Salvage gamma knife radiosurgery for active brain metastases from small-cell lung cancer after whole-brain radiation therapy: a retrospective multi-institutional study (JLKG1701).

Journal of neuro-oncology. 2020;147(1):67-76

Nakazaki K, Yomo S, Kondoh T, Serizawa T, Kenai H, Kawagishi J, Sato S, Nagano O, Aiyama H, Kawai H, Hasegawa T, Iwai Y, Nagatomo Y, Kida Y, Nishigaki M
PMID: 31933257 DOI: 10.1007/s11060-020-03397-9

PURPOSE: To evaluate the efficacy of gamma knife radiosurgery (GKS) for brain metastases (BMs) from small-cell lung cancer after whole-brain radiotherapy (WBRT). **METHODS:** We retrospectively analyzed the usefulness and safety of GKS in 163 patients from 15 institutions with 1-10 active BMs after WBRT. The usefulness and safety of GKS were evaluated using statistical methods. **RESULTS:** The median age was 66 years, and 79.1% of patients were men. The median number and largest diameter of BM were 2.0 and 1.4 cm, respectively. WBRT was administered prophylactically in 46.6% of patients. The median overall survival (OS) was 9.3 months, and the neurologic mortality was 20.0%. Crude incidences of local control failure and new lesion appearance were 36.6% and 64.9%, respectively. A BM diameter ≥ 1.0 cm was a significant risk factor for local progression (hazard ratio [HR] 2.556, $P = 0.039$) and neurologic death (HR 4.940, $P = 0.031$). Leukoencephalopathy at the final follow-up was more prevalent in the therapeutic WBRT group than in the prophylactic group ($P = 0.019$). The symptom improvement rate was 61.3%, and neurological function was preserved for a median of 7.6 months. Therapeutic WBRT was not a significant risk factor for OS, neurological death, local control, or functional deterioration ($P = 0.273$, 0.490, 0.779, and 0.560, respectively). Symptomatic radiation-related adverse effects occurred in 7.4% of patients. **CONCLUSIONS:** GKS can safely preserve neurological function and prevent neurologic death in patients with 1-10 small, active BMs after prophylactic and therapeutic WBRT.

[30] Impact of EGFR mutation and ALK rearrangement on the outcomes of non-small cell lung cancer patients with brain metastasis.

Neuro Oncol. 2020 Feb 20;22(2):267-277.

Balasubramanian SK, Sharma M, Venur VA, Schmitt P, Kotecha R, Chao ST, Suh JH, Angelov L, Mohammadi AM, Vogelbaum MA, Barnett GH, Jia X, Pennell NA, Ahluwalia MS
PMID: 31648302 DOI: 10.1093/neuonc/noz155

BACKGROUND: The impact of activating alterations in non-small cell lung cancer (NSCLC) (epidermal growth factor receptor [EGFR] mutation/anaplastic lymphoma kinase [ALK] translocation) in prognosticating patients with brain metastasis (BM) is not well defined. This study was sought to identify this impact in NSCLC patients with BM accounting for the known validated variables. **METHODS:** Among 1078 NSCLC-BM patients diagnosed/treated between January 1, 2000 and December 31, 2015, three hundred and forty-eight with known EGFR/ALK status were analyzed. Overall survival (OS) and intracranial progression-free survival (PFS) were measured from the time of BM. **RESULTS:** Ninety-one patients had either ALK ($n = 23$) alterations or EGFR ($n = 68$) mutation and 257 were wild type (WT; negative actionable mutations/alterations). Median age of EGFR/ALK+ NSCLC BM patients was 60 years (range 29.8-82.6 y) and ~50% ($n = 44$) had Karnofsky performance status (KPS) score >80 . Median number of BM was 2 (1 to ≥ 99). The median OS for the ALK/EGFR+ NSCLC BM was 19.9 versus 10.1 months for the WT ($P = 0.028$). The number of BM in the EGFR/ALK+ group did not impact OS (BM = 1 with 21.1 months vs 2-3 with 19.1 months and >3 with 23.7 months, $P = 0.74$), whereas fewer BM in the WT cohort had significantly better OS (BM = 1 with 13.8 mo, 2-3 with 11.0 mo and >3 with 8.1 mo; $P = 0.006$) with the adjustment of age, KPS, symptoms from BM and synchronicity. **CONCLUSIONS:** Number of BM does not impact outcomes in the EGFR/ALK+ NSCLC patients, implying that targeted therapy along with surgery and/or radiation may improve OS irrespective of the number of BM. Number of BM, extracranial metastasis (ECM), and KPS independently affected OS/PFS in WT NSCLC BM, which was consistent with the known literature.

[31] Estrogen, Progesterone and HER2 Receptor Discordance Between Primary Tumor and Brain Metastases in Breast Cancer and Its Effect on Treatment and Survival.

Neuro-oncology. 2020;

Sperduto PW, Mesko S, Li J, Cagney D, Aizer A, Lin NU, Nesbit E, Kruser TJ, Chan J, Braunstein S, Lee J, Kirkpatrick JP, Breen W, Brown PD, Shi D, Shih HA, Soliman H, Sahgal A, Shanley R, Sperduto W, Lou E, Everett A, Boggs DH, Masucci L, Roberge D, Remick J, Plichta K, Buatti JM, Jain S, Gaspar LE, Wu CC, Wang TJC, Bryant J, Chuong M, Yu J, Chiang V, Nakano T, Aoyama H, Mehta MP
PMID: 32034917 DOI: 10.1093/neuonc/noaa025

BACKGROUND: Breast cancer treatment is based on receptors for estrogen (ER), progesterone (PR) and human epidermal growth factor receptor 2 (HER2). At the time of metastasis, receptor status can be discordant from that at initial diagnosis. The purpose of this study was to determine the incidence of discordance and its effect on survival and subsequent treatment in patients with breast cancer brain metastases (BCBM). **METHODS:** A retrospective database of 316 patients who underwent craniotomy for BCBM between 2006 and 2017 was created. Discordance was considered present if the ER, PR or HER2 receptor status differed between the primary tumor and the BCBM. **RESULTS:** The overall receptor discordance rate was 132/316 (42%) and the subtype discordance rate was 100/316 (32%). Hormone receptors (HR, either ER or PR) were gained in 40/160 (25%) of patients with HR-negative primary tumors. HER2 was gained in 22/173 (13%) of patients with HER2-negative primary tumors. Subsequent treatment was not adjusted for most patients who gained receptors nonetheless median survival (MS) improved but did not reach statistical significance [HR (17 to 28 months, $p=0.12$), HER2 (15 to 19 months, $p=0.39$)]. MS for patients who lost receptors was worse [(HR (27 to 18 months, $p=0.02$), HER2 (30 to 18 months, $p=0.08$)]. **CONCLUSIONS:** Receptor discordance between primary tumor and BCBM is common, adversely affects survival if receptors are lost and represents a missed opportunity for use of effective treatments if receptors are gained. Receptor analysis of BCBM is indicated when clinically appropriate. Treatment should be adjusted accordingly.

[32] Postoperative stereotactic radiosurgery and hypofractionated radiotherapy for brain metastases using Gamma Knife and CyberKnife: a dual-center analysis.

Journal of neurosurgical sciences. 2020;

Kubler J, Wester-Ebbinghaus M, Wenz F, Stieler F, Bathen B, Mai SK, Wolff R, Hanggi D, Blanck O, Giordano F
PMID: 32031357 DOI: 10.23736/S0390-5616.20.04830-4

BACKGROUND: Postoperative stereotactic radiosurgery (SRS) and hypofractionated stereotactic radiotherapy (hFSRT) to tumor cavities is emerging as a new standard of care after resection of brain metastases. Both Gamma Knife (GK) and CyberKnife (CK) are modalities commonly used for stereotactic radiotherapy, but fractional schemes are not consistent. The objective of this study was to evaluate outcomes in patients receiving postoperative stereotactic radiotherapy of resected brain metastases (BM) using different fractionation schedules and modalities in two large centers. **METHODS:** Patients with newly diagnosed BM who underwent postoperative SRS or hFSRT with either GK or CK at two large cancer centers were retrospectively evaluated. We analyzed local control (LC), regional control (RC) and overall survival (OS). **RESULTS:** From 04/14 to 05/18 79 patients with 81 resection cavities were treated. Forty-seven patients (59.5%) received GK and 32 patients (40.5%) received CK treatment. Fifty-four cavities (66.7%) were treated with hFSRT and 27 (33.3%) with SRS. The most common hFSRT and SRS scheme was 3x10 Gy and 1x16 Gy, respectively. Median OS was 11.7 months with survival rates of 44.7% at 1 year and 18.5% at 2 years. LC was 83.3% after 1 year. Median time to regional progression was 12.0 months with RC rates of 61.1% at 6 months and 41.0% at 12 months. There was no difference in OS, LC or RC between GK and CK treatments or SRS and hFSRT. **CONCLUSIONS:** Both SRS and hFSRT provide high local control rates in resected BM regardless of the applied modality.

[33] Radiomics as prognostic factor in brain metastases treated with Gamma Knife radiosurgery.

Journal of neuro-oncology. 2020;146(3):439-449

Huang CY, Lee CC, Yang HC, Lin CJ, Wu HM, Chung WY, Shiau CY, Guo WY, Pan DH, Peng SJ

PMID: 32020474 DOI: 10.1007/s11060-019-03343-4

PURPOSE: Gamma Knife radiosurgery (GKRS) is a non-invasive procedure for the treatment of brain metastases. This study sought to determine whether radiomic features of brain metastases derived from pre-GKRS magnetic resonance imaging (MRI) could be used in conjunction with clinical variables to predict the effectiveness of GKRS in achieving local tumor control. **METHODS:** We retrospectively analyzed 161 patients with non-small cell lung cancer (576 brain metastases) who underwent GKRS for brain metastases. The database included clinical data and pre-GKRS MRI. Brain metastases were demarcated by experienced neurosurgeons, and radiomic features of each brain metastasis were extracted. Consensus clustering was used for feature selection. Cox proportional hazards models and cause-specific proportional hazards models were used to correlate clinical variables and radiomic features with local control of brain metastases after GKRS. **RESULTS:** Multivariate Cox proportional hazards model revealed that higher zone percentage (hazard ratio, HR 0.712; $P = .022$) was independently associated with superior local tumor control. Similarly, multivariate cause-specific proportional hazards model revealed that higher zone percentage (HR 0.699; $P = .014$) was independently associated with superior local tumor control. **CONCLUSIONS:** The zone percentage of brain metastases, a radiomic feature derived from pre-GKRS contrast-enhanced T1-weighted MRIs, was found to be an independent prognostic factor of local tumor control following GKRS in patients with non-small cell lung cancer and brain metastases. Radiomic features indicate the biological basis and characteristics of tumors and could potentially be used as surrogate biomarkers for predicting tumor prognosis following GKRS.

[34] The effect of Gamma Knife radiosurgery on large posterior fossa metastases and the associated mass effect from peritumoral edema.

Journal of neurosurgery. 2020;:1-9

Muhsen BA, Joshi KC, Lee BS, Thapa B, Borghei-Razavi H, Jia X, Barnett GH, Chao ST, Mohammadi AM, Suh JH, Vogelbaum MA, Angelov L

PMID: 31978879 DOI: 10.3171/2019.11.JNS191485

OBJECTIVE: Gamma Knife radiosurgery (GKRS) as monotherapy is an option for the treatment of large ($>= 2$ cm) posterior fossa brain metastases (LPFMs). However, there is concern regarding possible posttreatment increase in peritumoral edema (PTE) and associated compression of the fourth ventricle. This study evaluated the effects and safety of GKRS on tumor and PTE control in LPFM. **METHODS:** The authors performed a single-center retrospective review of 49 patients with 51 LPFMs treated with GKRS. Patients with at least 1 clinical and radiological follow-up visit were included. Tumor, PTE, and fourth ventricle volumetric measurements were used to assess efficacy and safety. Overall survival was a secondary outcome. **RESULTS:** Fifty-one lesions in 49 consecutive patients were identified; 57.1% of patients were male. At the time of GKRS, the median age was 61.5 years, and the median Karnofsky Performance Status score was 90. The median number of LPFMs and overall brain metastases were 1 and 2, respectively. The median overall tumor, PTE, and fourth ventricle volumes at diagnosis were 4.96 cm³ (range 1.4-21.1 cm³), 14.98 cm³ (range 0.6-71.8 cm³), and 1.23 cm³ (range 0.3-3.2 cm³), respectively, and the median lesion diameter was 2.6 cm (range 2.0-5.07 cm). The median follow-up time was 7.3 months (range 1.6-57.2 months). At the first follow-up, 2 months posttreatment, the median tumor volume decreased by 58.66% (range -96.95% to +48.69%, $p < 0.001$), median PTE decreased by 78.10% (range -99.92% to +198.35%, $p < 0.001$), and the fourth ventricle increased by 24.97% (range -37.96% to +545.6%, $p < 0.001$). The local control rate at first follow-up was 98.1%. The median OS was 8.36 months. No patient required surgical intervention, external ventricular drainage, or shunting between treatment and first follow-up. However, 1 patient required a ventriculoperitoneal shunt at 23 months from treatment. Posttreatment, 65.30%

received our general steroid taper, 6.12% received no steroids, and 28.58% required prolonged steroid treatment. **CONCLUSIONS:** In this retrospective analysis, patients with LPFMs treated with GKRS had a statistically significant posttreatment reduction in tumor size and PTE and marked opening of the fourth ventricle (all $p < 0.001$). This study demonstrates that GKRS is well tolerated and can be considered in the management of select cases of LPFMs, especially in patients who are poor surgical candidates.

[35] Referral Patterns and Outcome of Patients With Synchronous Brain Metastases From Non-small Cell Lung Cancer Treated With Gamma Knife Radiosurgery in a Third-Line Treatment Centre in The Netherlands - A Retrospective Analysis.

Clinical oncology (Royal College of Radiologists (Great Britain)). 2020;32(1):52-59

Ten Berge DMHJ, Aarts MJ, Hanssens PEJ, Beute GN, Aerts JGJV, Kloover JS

PMID: 31345622 DOI: 10.1016/j.clon.2019.07.004

AIMS: Little understanding exists of referral patterns for patients with brain metastasis from non-small cell lung cancer (NSCLC) towards treatment with Gamma Knife radiosurgery (GKRS). Therefore, we explored current clinical daily practice and prognosis. **MATERIAL AND METHODS:** In total, 1129 patients with synchronously diagnosed brain metastasis from NSCLC diagnosed between 2008 and 2014 were selected from the population-based Netherlands Cancer Registry; 242 patients were treated with GKRS. **RESULTS:** Patients receiving GKRS were younger (62 years versus 64 years) and had lower tumour burden: the presence of T2 was higher and T4 was lower (43% versus 33%; $P = 0.0158$, 19% versus 28%; $P = 0.0044$, respectively). They more frequently had cN0 (32% versus 19%; $P </= 0.0001$), less frequently had N3 disease (18% versus 29%; $P = 0.0004$) and there were fewer metastatic sites. In multivariable logistic regression analysis, only age $</= 60$ years (odds ratio 1.4; 95% confidence interval 1.0-2.0) and patients with N0 stage, compared with those with N2, N3 and NX (odds ratio 0.6 [0.4-0.9], 0.3 [0.2-0.6], 0.3 [0.1-0.6], respectively), were more likely to receive GKRS. Gender, T-stage, histology, number of comorbidities, country of birth as proxy for ethnicity and socioeconomic status were not associated. The median survival was 9.6 months after GKRS versus 4.0 months in the noGKRS group (Log-rank: $P </= 0.0001$). Multivariable, GKRS, female, lower T-/N-stage, < 2 comorbidities, adenocarcinoma and higher socioeconomic status were associated with a significantly reduced hazard of death. For the patients with at least one follow-up magnetic resonance image (80%), local intracranial tumour control was achieved in 93% at the last follow-up. **CONCLUSION:** Patients presenting with synchronic brain metastasis from NSCLC who are referred to a third-line treatment centre for GKRS are younger and have a lower tumour load. Due to a high level of local control, GKRS is able to provide a significant window of opportunity for additional treatment of the primary tumour.

[36] Evidence of dose-response following hypofractionated stereotactic radiotherapy to the cavity after surgery for brain metastases.

Journal of neuro-oncology. 2020;146(2):357-362

Garimall S, Shanker M, Johns E, Watkins T, Olson S, Huo M, Foote MC, Pinkham MB

PMID: 31907796 DOI: 10.1007/s11060-019-03383-w

BACKGROUND AND OBJECTIVE: A retrospective review of consecutive patients between January 2012 and December 2018 receiving hypofractionated stereotactic radiotherapy (HSRT) to the cavity after resection for brain metastases was performed. **METHODS:** Treatment was delivered using an appropriately commissioned linear accelerator. The primary outcome was time to radiological or histological confirmation of local recurrence following completion of HSRT. Dose-fractionation regimens were converted to biologically 2 Gy-equivalent doses assuming alpha/beta = 10 (EQD2[10]). Multivariate Cox proportional hazards modelling was performed to determine hazard ratios (HR) with respective 95% confidence intervals (CI). The Log-rank test was used to determine p values taking statistical significance $p < 0.05$. **RESULTS:** There were 134 patients and 144 cavities identified. The most common primary histologies were melanoma

(n = 49) and lung (n = 32). 116 patients (87%) underwent a gross total resection. Median planning target volume (PTV) was 28 cm³ (range 2.4-149.2). Median EQD2[10] was 38.4 Gy (range 22.3-59.7) and 24 Gy in 3 fractions was the most common regimen. 12 (9%) patients demonstrated local recurrence at median interval 215 days (range 4-594). 7 (5%) patients experienced grade 3 or higher toxicities. In multivariate analysis, EQD2[10] was associated with local failure such that increased equivalent doses improved local control [HR = 0.79 and 95% CI 0.65-0.96, p = 0.0192]. There were no significant associations for primary histology, patient age, volume of residual disease, PTV volume or location. **CONCLUSION:** This large series demonstrates that HSFRT to the surgical resection cavity for brain metastases has improved local control with increasing dose. Rates of grade 3 or higher toxicity were low overall.

[37] Impact of brain metastasis velocity on neurologic death for brain metastasis patients experiencing distant brain failure after initial stereotactic radiosurgery.
Journal of neuro-oncology. 2020;146(2):285-292

LeCompte MC, Hughes RT, Farris M, Masters A, Soike MH, Lanier C, Glenn C, Cramer CK, Watabe K, Su J, Ruiz J, Whitlow CT, Wang G, Laxton AW, Tatter SB, Chan MD

PMID: 31894518 DOI: 10.1007/s11060-019-03368-9

PURPOSE: Patients with high rates of developing new brain metastases have an increased likelihood of dying of neurologic death. It is unclear, however, whether this risk is affected by treatment choice following failure of primary stereotactic radiosurgery (SRS). **METHODS:** From July 2000 to March 2017, 440 patients with brain metastasis were treated with SRS and progressed to have a distant brain failure (DBF). Eighty-seven patients were treated within the immunotherapy era. Brain metastasis velocity (BMV) was calculated for each patient. In general, the institutional philosophy for use of salvage SRS vs whole brain radiotherapy (WBRT) was to postpone the use of WBRT for as long as possible and to treat with salvage SRS when feasible. No further treatment was reserved for patients with poor life expectancy and who were not expected to benefit from salvage treatment. **RESULTS:** Two hundred and eighty-five patients were treated with repeat SRS, 91 patients were treated with salvage WBRT, and 64 patients received no salvage radiation therapy. One-year cumulative incidence of neurologic death after salvage SRS vs WBRT was 15% vs 23% for the low- (p = 0.06), 30% vs 37% for the intermediate- (p < 0.01), and 31% vs 48% (p < 0.01) for the high-BMV group. Salvage WBRT was associated with increased incidence of neurologic death on multivariate analysis (HR 1.64, 95% CI 1.13-2.39, p = 0.01) when compared to repeat SRS. One-year cumulative incidence of neurologic death for patients treated within the immunotherapy era was 9%, 38%, and 38% for low-, intermediate-, and high-BMV groups, respectively (p = 0.01). **CONCLUSION:** Intermediate and high risk BMV groups are predictive of neurologic death. The association between BMV and neurologic death remains strong for patients treated within the immunotherapy era.

2019

[38] Stereotactic Radiosurgery to More Than 10 Brain Metastases: Evidence to Support the Role of Radiosurgery for Ideal Hippocampal Sparing in the Treatment of Multiple Brain Metastases.

World neurosurgery. 2019;135:e174-e180

Susko MS, Garcia MA, Ma L, Nakamura JL, Raleigh DR, Fogh S, Theodosopoulos P, McDermott M, Sneed PK, Braunstein SE

PMID: 31785436 DOI: 10.1016/j.wneu.2019.11.089

BACKGROUND: Brain metastases are a common occurrence, with literature supporting the treatment of a limited number of brain metastases with stereotactic radiosurgery (SRS), as opposed to whole brain radiotherapy (WBRT). Less well understood is the role of SRS in patients with ≥ 10 brain metastases. **METHODS:** Patients treated with SRS to ≥ 10 brain metastases

without concurrent WBRT between March 1999 and December 2016 were reviewed. Analysis was performed for overall survival, treated lesion freedom from progression (FFP), freedom from new metastases (FFNMs), and adverse radiation effect. Hippocampal volumes were retrospectively generated in patients treated with up-front SRS for evaluation of dose volume metrics. **RESULTS:** A total of 143 patients were identified with 75 patients having up-front SRS and 68 patients being treated as salvage therapy after prior WBRT. The median number of lesions per patient was 13 (interquartile range [IQR], 11-17). Median total volume of treatment was 4.1 cm³ (IQR, 2.0-9.9 cm³). The median 12-month FFP for up-front and salvage treatment was 96.8% (95% confidence interval [CI], 95.5-98.1) and 83.6% (95% CI, 79.9-87.5), respectively (P < 0.001). Twelve-month FFNMs for up-front and salvage SRS was 18.8% (95% CI, 10.9-32.3) versus 19.2% (95% CI, 9.7-37.8), respectively (P = 0.90). The mean hippocampal dose was 150 cGy (IQR, 100-202 cGy). **CONCLUSIONS:** Excellent rates of local control can be achieved when treating patients with >10 intracranial metastases either in the up-front or salvage setting. Hippocampal sparing is readily achievable with expected high rates of new metastatic lesions in treated patients.

[39] Pathologic Correlation of Cellular Imaging Using Apparent Diffusion Coefficient Quantification in Patients with Brain Metastases After Gamma Knife Radiosurgery.

World neurosurgery. 2019;134:e903-e912

Borghesi-Razavi H, Sharma M, Emch T, Krivosheya D, Lee B, Muhsen B, Prayson R, Obuchowski N, Barnett GH, Vogelbaum MA, Chao ST, Suh JH, Mohammadi AM, Angelov L

PMID: 31733389 DOI: 10.1016/j.wneu.2019.11.037

OBJECTIVE: To evaluate the role of apparent diffusion coefficient (ADC) in differentiating radiation necrosis (RN) from recurrent tumor after Gamma Knife radiosurgery (GKRS) for brain metastases (BMs). **METHODS:** Forty-one patients with BM who underwent surgical intervention after GKRS at Cleveland Clinic (2006-2017) were included in this retrospective study. The ADC values of the growing lesions and the contralateral hemisphere were calculated using picture archiving and communication system. These values were correlated to the percentage of RN identified on pathologic evaluation of the surgical specimen. **RESULTS:** The median age of the patients was 59 years (range, 25-86 years), and lung cancer (63.4%) was the most common malignancy. Median initial (pre-GKRS) target volume of the lesions was 5.4 cc (range, 0.135-45.6 cc), and median GKRS dose was 18.0 Gy. Surgical resection or biopsy was performed at a median of 176 days after GKRS. Two variables were statistically significant predictors of predominant RN (75%-100%) in the surgical specimen: 1) ADC of the lesion on the preresection magnetic resonance imaging (MRI) and 2) initial pre-GKRS target volume. ADC $>1.5 \times 10^{-3}$ mm²/s within the lesion on MRI predicted significant RN on pathologic evaluation of the lesion (P < 0.05). Similarly, when the target volume before GKRS was large (>10 cc), the risk of identifying significant necrosis in the pathologic specimen was elevated (P < 0.05). **CONCLUSIONS:** Our data suggest that the combination of lesion ADC on MRI prior to surgical intervention and the initial target volume can predict RN with reasonable accuracy.

[40] Extent of surrounding edema does not correlate with acute complications after radiosurgery for melanoma brain metastases.

Journal of neuro-oncology. 2019;145(3):581-585

Jardim A, Scott J, Drew Z, Foote MC, Sadasivan AP, Hall B, Olson SL, Shanker M, Pinkham MB

PMID: 31691060 DOI: 10.1007/s11060-019-03330-9

AIM: To assess whether extent of surrounding edema correlates with acute adverse clinical outcomes within 3 months after stereotactic radiosurgery (SRS) for melanoma brain metastases (BM). **METHODS:** Patients with melanoma BM treated with SRS were included in a single center retrospective analysis. A contrast-enhanced magnetic resonance image (MRI) brain was acquired on the day of treatment and used to calculate the volume of the largest lesion (the index BM) and total volume of all BM. Their corresponding volume of surrounding

edema was defined based on the fluid attenuated inversion recovery (FLAIR) sequence. After SRS, MRI was performed every 3 months for at least 2 years if the patient remained well enough to do so. Adverse neurologic events after SRS were defined using common terminology criteria for adverse events (CTCAE) version 5.0. Multivariate regression analyses assessed for associations between BM size and edema at baseline with increasing edema and neurologic adverse events within 3 months after SRS. **RESULTS:** Mean volume of the index BM reduced from 2.2 to 0.5 cm³ at 3 months after SRS ($p = 0.03$). Mean volume of edema surrounding the index BM was 6.4 cm³ at baseline, 10.2 cm³ at 3 months and 5.5 cm³ at 6 months. There were 7/43 (16%) patients that experienced an adverse neurological event within 3 months (attributable to any cause) and 4/43 (9%) were associated with an increase in BM edema. On univariate and multivariate analyses, there were no correlations between any baseline factors and volume of edema at 3 months. However, SRS dose delivered and systemic therapy use within 4 weeks of SRS both correlated with a reduction in edema surrounding the index BM.

CONCLUSION: A transient increase in mean volume of edema was apparent at 3 months after SRS. However, this resolved by 6 months and did not correlate with adverse events or dexamethasone requirement. Thus, the clinical significance is uncertain.

[41] Cranial Irradiation for Patients with Epidermal Growth Factor Receptor (EGFR) Mutant Lung Cancer Who Have Brain Metastases in the Era of a New Generation of EGFR Inhibitors.

The oncologist. 2019;24(12):e1417-e1425

Lee JH, Chen HY, Hsu FM, Chen JS, Liao WY, Shih JY, Yu CJ, Chen KY, Tsai TH, Yang JC

PMID: 31127020 DOI: 10.1634/theoncologist.2019-0152

BACKGROUND: Immediate whole brain radiation (WBRT) has been the standard for patients with lung cancer with brain metastases. The study aims to evaluate the effect of immediate cranial irradiation in patients with epidermal growth factor receptor (EGFR) mutant lung cancer in the era of a new generation of EGFR inhibitors. **MATERIALS AND METHODS:** Medical records of 198 patients with EGFR mutant non-small cell lung cancer and brain metastases at initial metastatic diagnosis were reviewed. Patients were categorized into four groups: immediate WBRT, immediate cranial stereotactic radiosurgery (SRS), delayed radiation upon progression of cranial lesions (DRT), and never cranial irradiation (NRT). Overall survival (OS) and progression-free survival related to EGFR inhibitors were analyzed. **RESULTS:** The SRS group had the fewest brain metastases and fewest extracranial lesions, and the DRT and NRT groups had the smallest brain metastases. Median survival were 18.5, 55.7, 21.1, and 18.2 months for the WBRT, SRS, DRT, and NRT groups, respectively. Patients who had received EGFR T790M inhibitors survived longer (41.1 vs. 19.8 months). In multivariate analysis, the OS of patients in the SRS group was longer than that in the NRT group (adjusted hazard ratio [aHR]: 0.315). Patients who had fewer extracranial lesions and who had received EGFR T790M inhibitor treatments also survived longer (aHR: 0.442 and 0.357, respectively). **CONCLUSION:** Immediate stereotactic radiosurgery but not whole brain radiation was associated with longer survival. Because of patient heterogeneity and the introduction of EGFR T790M inhibitors, the timing and modality of cranial irradiation should be determined individually, and cranial irradiation may be omitted for selected patients. **IMPLICATIONS FOR PRACTICE:** Immediate whole brain radiation has been the standard for patients with lung cancer with brain metastases. In this study, it was observed that, for patients with epidermal growth factor receptor (EGFR) mutant advanced lung cancer who had brain metastases, there was no difference in survival between patients who never received cranial irradiation and those who received whole brain radiation immediately. Patients who received immediate stereotactic radiosurgery or who had ever received EGFR T790M inhibitors survived longer. Patients who received immediate stereotactic radiosurgery have fewer brain metastases. These findings suggest that the timing and modality of cranial irradiation should be determined individually, and cranial irradiation may be omitted in selected patients.

[42] Repeat stereotactic radiosurgery for the management of locally recurrent brain metastases.

Journal of neuro-oncology. 2019;145(3):551-559

lorio-Morin C, Mercure-Cyr R, Figueiredo G, Touchette CJ, Masson-Cote L, Mathieu D
PMID: 31667732 DOI: 10.1007/s11060-019-03323-8

PURPOSE: Stereotactic radiosurgery (SRS) is a well-established treatment option for brain metastases (BM). Repeat SRS for progressive BM is an increasingly used paradigm, although little data is available to support this practice. The goal of this study was to assess the safety and efficacy of a second SRS procedure on a previously treated BM. **METHODS:** We performed a retrospective metastasis-level analysis of patients who underwent two SRS procedures on the same lesion and for whom at least 6 months of radiological follow-up was available. The data collected included patient characteristics, clinical symptoms at time of treatment, SRS parameters, radiological response per RANO-BM criteria, clinical evolution and survival. **RESULTS:** Seventy-five BM in 56 patients were included in the analysis. Most frequent primary histologies were non-small-cell lung cancer (59%) and breast cancer (19%). At the second SRS, median treatment volume was 1.19 cc (range 0.07-20.6) treated with a median margin dose of 18 Gy (range 12-20) at the 50% isodose line (range 30-80%). Median follow-up was 11 months. Progression per RANO-BM criteria occurred in 31%, yielding actuarial local control at 1, 2, and 5 years of 68%, 54% and 54% respectively. At last follow-up, 10 patients (18%) had improved relative to the initial presentation, while 21 (38%) were stable and 25 (44%) were deteriorated. Radiation-induced edema and radionecrosis occurred in 8.3% and 5% respectively. The median survival from the diagnosis of BM was 30 months. **CONCLUSION:** Repeat SRS is a safe and effective novel therapeutic approach to consider in carefully selected patients.

[43] Cognitive functioning and predictors thereof in patients with 1-10 brain metastases selected for stereotactic radiosurgery.

Journal of neuro-oncology. 2019;145(2):265-276

Schimmel WCM, Gehring K, Hanssens PEJ, Sitskoorn MM

PMID: 31552588 DOI: 10.1007/s11060-019-03292-y

PURPOSE: Information on predictive factors of cognitive functioning in patients with (multiple) brain metastases (BM) selected for radiosurgery may allow for more individual care and may play a role in predicting cognitive outcome after radiosurgery. The aim of this study was to evaluate cognitive performance, and predictors thereof, in patients with 1-10 BM before radiosurgery.

METHODS: Cognition was measured before radiosurgery using a standardized neuropsychological test battery in patients with 1-10 BM (expected survival > 3 months; KPS \geq 70; no prior BM treatment). Regression formulae were constructed to calculate sociodemographically corrected z scores. Group and individual cognitive functioning was analyzed. Multivariable regression was used to explore potential predictors. **RESULTS:** Patients (N = 92) performed significantly worse than controls (N = 104) on all 11 test variables (medium-large effect sizes for 8 variables). Percentages of impairment were highest for information processing (55.3%), dexterity (43.2%) and cognitive flexibility (28.7%). 62% and 46% of patients had impairments in at least two, or three test variables, respectively. Models including combinations of clinical and psychological variables were predictive of verbal memory, psychomotor speed, information processing and dexterity. Neither number nor volume of metastases predicted patients' test performance. **CONCLUSIONS:** Already before radiosurgery, almost half of the patients suffered from severe cognitive deficits in at least three test variables. At group and individual level, information processing, cognitive flexibility, and dexterity were most affected. These cognitive impairments may impair daily functioning and patients' ability to make (shared) treatment decisions. Both clinical (symptomatic BM; timing of BM diagnosis) and psychological (mental fatigue) characteristics influenced cognitive performance. **CLINICAL TRIAL INFORMATION:** Cognition and Radiation Study A (CAR-Study A; ClinicalTrials.gov Identifier: NCT02953756; Medical Ethics Committee file number: NL53472.028.15/P1515).

[44] Single- versus 2-session Gamma Knife surgery for symptomatic midsize brain metastases: a propensity score-matched analysis.

Journal of neurosurgery. 2019;:1-9

Yomo S, Oda K, Oguchi K

PMID: 31628290 DOI: 10.3171/2019.7.JNS191193

OBJECTIVE: Two-session Gamma Knife surgery (GKS) has recently been demonstrated to be an effective and less-invasive alternative for large brain metastases not treatable by microsurgical resection. This raises the clinical question of whether the 2-session GKS strategy further improves treatment outcomes for patients with symptomatic midsize brain metastases (2-10 cm³) as compared to single-session GKS. The present study aimed to compare the local therapeutic effects and toxicities of single-session and 2-session GKS for treating these lesions. **METHODS:** Patients with focal neurological deficits attributable to midsize brain metastases who underwent upfront GKS during the period from 2010 to 2018 were retrospectively identified from an institutional database. Patients for whom both post-GKS imaging studies and neurological evaluations from outpatient visits were available were eligible. Using propensity score-matching (PSM) analysis, unique matched pairs which had a similar likelihood of receiving 2-session GKS were generated. The main outcome measure was a composite of imaging and/or neurological worsening of the lesion of interest. Functional improvement and overall survival (OS) were also compared between the 2 treatment arms. **RESULTS:** In total, 219 cancer patients with 252 symptomatic midsize brain metastases were eligible. Of these 252 tumors, 176 and 76 were treated with single- and 2-session GKS, respectively. After PSM, 68 pairs of tumors were obtained. The Gray test showed that 2-session GKS achieved a longer local progression-free interval than single-session GKS (1-year local control rate: 84% vs 53%; HR 0.31, 95% CI 0.16-0.63, p = 0.001). Two-session GKS was also associated with greater functional improvement in KPS scores (mean 18.3 +/- 14.6 vs 12.8 +/- 14.1, p = 0.040). The median OS did not differ significantly between single- and 2-session GKS (15.6 vs 24.7 months; HR 0.69, 95% CI 0.44-1.10, p = 0.11). **CONCLUSIONS:** Two-session GKS achieved more durable local tumor control and greater functional improvement than single-session GKS for patients with symptomatic midsize brain metastases, although there was no OS advantage.

[45] Do brain mets grow while you wait? A volumetric natural history assessment of brain metastases from time of diagnosis to gamma knife treatment.

Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2019;68:117-122

Plunkett RJ, Barone TA, Brady WE, Attwood KM, Prasad D

PMID: 31340886 DOI: 10.1016/j.jocn.2019.07.019

Brain metastasis (BM) is a common neurologic complication of cancers such as lung, breast, and melanoma. Recently, there has been a shift in treatment of BM from whole brain radiation therapy to stereotactic radiosurgery (SRS) and the success is dependent on tumor volume. While most metastases grow over time, data on growth rate is lacking. Therefore, we document volume changes of metastases before treatment. We retrospectively reviewed MRI imaging records of 82 patients with a total of 294 BMs, treated in our cancer center by one neurosurgeon and one radiation oncologist with Gamma Knife SRS over a three-year period. We measured tumor volume at the time of diagnosis and compared with tumor volume on the day of treatment. Volumes were compared using the Wilcoxon signed-rank test. Lung, melanoma and breast made up the majority of metastases diagnosed. More than 75% of tumors grew and these changes in volume and percent changes in volume were statistically significant. Thirty percent of tumors doubled in size before treatment. Patients with the largest mean pretreatment tumor size were urgently treated within 6 days, yet still demonstrated the largest change in volume. This study is one of the first to document volume changes of brain metastases from the time of diagnosis to SRS treatment. Our results indicate that brain metastases can grow rapidly and it is imperative that we streamline patient management processes to minimize delays in treating patients with SRS, since outcomes are dependent on tumor size.

[46] Single-fraction versus hypofractionated stereotactic radiosurgery for medium-sized brain metastases of 2.5 to 3 cm.

Journal of neuro-oncology. 2019;145(1):49-56

Chon H, Yoon K, Lee D, Kwon DH, Cho YH

PMID: 31420793 DOI: 10.1007/s11060-019-03265-1

PURPOSE: Given recently suggested utility of hypofractionated stereotactic radiosurgery (SRS) in treating large brain metastases (BMs) > 3 cm, we sought to prospectively control tumor size variable to investigate the efficacy and safety of hypofractionated SRS for medium-sized BMs (2.5 to 3 cm) compared with single-fraction SRS. **METHODS:** Between 2011 and 2015, a total of 100 patients with newly diagnosed BMs (n = 105) of 2.5 to 3 cm had been treated with either single-fraction (n = 67; median dose 20 Gy) or hypofractionated SRS (n = 38; median cumulative dose 35 Gy in 5 daily fractions). No patients received any prior or upfront whole brain radiotherapy. In each patient, treatment outcome was measured by local tumor control (LTC), overall and progression-free survival (OS and PFS), and the occurrence of radiation necrosis (RN). **RESULTS:** With a median follow-up of 14 months, significant differences were observed between the single-fraction versus hypofractionated SRS groups in the incidence of RN (29.9% vs. 5.3%, P < 0.001) and LTC (1-year LTC rates 66.6% vs. 92.4%, P = 0.028). There were no differences in PFS (median 6 months vs. 6 months, P = 0.381) and OS (median 13 months vs. 18 months, P = 0.239). Treatment-related adverse events (>= grade 2 toxicity by CTCAE ver. 4.0) occurred more frequently in single-fraction group, although the difference did not reach statistical significance (56.3% vs. 36.1%, P = 0.084). **CONCLUSIONS:** Our results suggest a better safety and efficacy profile of hypofractionated SRS for medium-sized BMs compared with single-fraction SRS. Further prospective studies are needed to confirm these results.

[47] The impact of EGFR-TKI use on clinical outcomes of lung adenocarcinoma patients with brain metastases after Gamma Knife radiosurgery: a propensity score-matched analysis based on extended JLGK0901 dataset (JLGK0901-EGFR-TKI).

Journal of neuro-oncology. 2019;145(1):151-157

Yomo S, Serizawa T, Yamamoto M, Higuchi Y, Sato Y, Shuto T, Akabane A, Jokura H, Kawagishi J, Aoyama H

PMID: 31487030 DOI: 10.1007/s11060-019-03282-0

PURPOSE: Recent advances in targeted therapy have prolonged overall survival (OS) for patients with lung cancer. The impact of epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI) on brain metastases (BM) treated with stereotactic radiosurgery (SRS) has not, however, been fully elucidated. We investigated the influence of post-SRS EGFR-TKI use on the efficacy and toxicity of SRS for BM from lung adenocarcinoma. **METHODS:** We used the updated dataset of the Japanese Leksell Gamma Knife (JLGK) 0901 study, which proved the efficacy of Gamma Knife SRS in patients with BM. Propensity score matching (PSM) analysis was employed to determine the impact of concurrent or post-SRS EGFR-TKI use on OS, neurological death, intracranial disease recurrence and SRS-related adverse events. **RESULTS:** Among 1194 patients registered in the JLGK0901 study, 608 eligible lung adenocarcinoma patients were identified and 238 (39%) had received EGFR-TKI concurrently or during the post-SRS clinical course. After PSM, there were 200 patient pairs with/without post-SRS EGFR-TKI use. EGFR-TKI use was associated with longer OS (median 25.5 vs. 11.0 months, HR 0.60, 95% CI 0.48-0.75, p < 0.001), although the long-term OS curves eventually crossed. Distant intracranial recurrence was more likely in patients receiving EGFR-TKI (HR 1.45, 95% CI 1.12-1.89, p = 0.005). Neurological death, local recurrence and SRS-related adverse event rates did not differ significantly between the two groups. **CONCLUSIONS:** Although patients receiving EGFR-TKI concurrently or after SRS had significantly longer OS, the local treatment efficacy and toxicity of SRS did not differ between patients with/without EGFR-TKI use.

[48] Outcome of three-fraction gamma knife radiosurgery for brain metastases according to fractionation scheme: preliminary results.

Journal of neuro-oncology. 2019;145(1):65-74

Jeon C, Cho KR, Choi JW, Kong DS, Seol HJ, Nam DH, Lee JI
PMID: 31446529 DOI: 10.1007/s11060-019-03267-z

PURPOSE: The optimal interfraction intervals for fractionated radiosurgery has yet to be established. We investigated the outcome of fractionated gamma knife radiosurgery (FGKRS) for large brain metastases (BMs) according to different interfraction intervals. **METHODS:** Between September 2016 and May 2018, a total of 45 patients who underwent FGKRS for BMs were enrolled in this study. They were divided into two groups (standard fractionation over 3 consecutive days with a 24-h interfraction interval versus prolonged fractionation over 4 or 5 days with an interfraction interval of at least 48-h). BMs with ≥ 2 cm in maximum diameter or ≥ 5 cm³ in volume were included in analysis. **RESULTS:** Among 52 BMs treated with 3-fraction GKRS, 25 (48.1%) were treated with standard fractionation scheme, and 27 (51.9%) with prolonged fractionation scheme. The median follow-up period was 10.5 months (range 5-25). Local tumor control rates of the standard group were 88.9% at 6 months and 77.8% at 12 months, whereas those of the prolonged group were 100% at 6 and 12 months ($p = 0.023$, log-rank test). In multivariate analysis, fractionation scheme (hazard ratio [HR] 0.294, 95% CI 0.099-0.873; $p = 0.027$) and tumor volume (HR 0.200, 95% CI 0.051-0.781; $p = 0.021$) were revealed as the only significant factors affecting the local tumor control after 3-fraction GKRS. **CONCLUSIONS:** Our preliminary tumor control results suggest a promising role of 3-fraction GKRS with an interfraction interval of at least 48-h. This fractionation regimen could be an effective and safe treatment option in the management of large BMs.

[49] Estimating survival in patients with gastrointestinal cancers and brain metastases: An update of the graded prognostic assessment for gastrointestinal cancers (GI-GPA).

Clinical and translational radiation oncology. 2019;18:39-45

Sperduto PW, Fang P, Li J, Breen W, Brown PD, Cagney D, Aizer A, Yu JB, Chiang V, Jain S, Gaspar LE, Myrehaug S, Sahgal A, Braunstein S, Sneed P, Cameron B, Attia A, Molitoris J, Wu CC, Wang TJC, Lockney NA, Beal K, Parkhurst J, Buatti JM, Shanley R, Lou E, Tandberg DD, Kirkpatrick JP, Shi D, Shih HA, Chuong M, Saito H, Aoyama H, Masucci L, Roberge D, Mehta MP
PMID: 31341974 DOI: 10.1016/j.ctro.2019.06.007

BACKGROUND: Patients with gastrointestinal cancers and brain metastases (BM) represent a unique and heterogeneous population. Our group previously published the Diagnosis-Specific Graded Prognostic Assessment (DS-GPA) for patients with GI cancers (GI-GPA) (1985-2007, $n=209$). The purpose of this study is to update the GI-GPA based on a larger contemporary database. **METHODS:** An IRB-approved consortium database analysis was performed using a multi-institutional (18), multi-national (3) cohort of 792 patients with gastrointestinal (GI) cancers, with newly-diagnosed BM diagnosed between 1/1/2006 and 12/31/2017. Survival was measured from date of first treatment for BM. Multiple Cox regression was used to select and weight prognostic factors in proportion to their hazard ratios. These factors were incorporated into the updated GI-GPA. **RESULTS:** Median survival (MS) varied widely by primary site and other prognostic factors. Four significant factors (KPS, age, extracranial metastases and number of BM) were used to formulate the updated GI-GPA. Overall MS for this cohort remains poor; 8months. MS by GPA was 3, 7, 11 and 17months for GPA 0-1, 1.5-2, 2.5-3.0 and 3.5-4.0, respectively. $>30\%$ present in the worst prognostic group (GI-GPA of ≤ 1.0). **CONCLUSIONS:** Brain metastases are not uncommon in GI cancer patients and MS varies widely among them. This updated GI-GPA index improves our ability to estimate survival for these patients and will be useful for therapy selection, end-of-life decision-making and stratification for future clinical trials. A user-friendly, free, on-line app to calculate the GPA score and estimate survival for an individual patient is available at brainmetgpa.com.

[50] Immunotherapy is associated with improved survival and decreased neurologic death after SRS for brain metastases from lung and melanoma primaries.

Neuro-oncology practice. 2019;6(5):402-409

Lanier CM, Hughes R, Ahmed T, LeCompte M, Masters AH, Petty WJ, Ruiz J, Triozzi P, Su J, O'Neill S, Watabe K, Cramer CK, Laxton AW, Tatter SB, Wang G, Whitlow C, Chan MD
PMID: 31555455 DOI: 10.1093/nop/npz004

BACKGROUND: The effect of immunotherapy on brain metastasis patients remains incompletely understood. Our goal was to evaluate its effect on survival, neurologic death, and patterns of failure after stereotactic radiosurgery (SRS) without prior whole-brain radiation therapy (WBRT) in patients with lung and melanoma primaries metastatic to the brain. **METHODS:** We performed a retrospective analysis of 271 consecutive lung or melanoma patients treated with upfront SRS for brain metastases between 2013 and 2018. Of these patients, 101 (37%) received immunotherapy and 170 (63%) did not. Forty-three percent were treated with nivolumab. Thirty-seven percent were treated with pembrolizumab. Fifteen percent were treated with ipilimumab. One percent were treated with a combination of nivolumab and ipilimumab. One percent were treated with atezolizumab. Three percent were treated with another immunotherapy regimen. Survival was estimated by the Kaplan-Meier method and cumulative incidences of neurologic death, and local and distant brain failure were estimated using death as a competing risk. **RESULTS:** The median overall survival (OS) of patients treated with immunotherapy vs without was 15.9 (95% CI: 13.3 to 24.8) vs 6.1 (95% CI: 5.1 to 8.8) months ($P < .01$). The 1-year cumulative incidence of neurologic death was 9% in patients treated with immunotherapy vs 23% in those treated without ($P = .01$), while nonneurologic death was not significantly different (29% vs 41%, $P = .51$). Median brain metastasis velocity (BMV) did not differ between groups, and rates of salvage SRS and WBRT were similar. **CONCLUSIONS:** The use of immunotherapy in patients with lung cancer or melanoma metastatic to the brain treated with SRS is associated with improved OS and decreased incidence of neurologic death.

[51] Multidimensional assessment of fatigue in patients with brain metastases before and after Gamma Knife radiosurgery.

Journal of neuro-oncology. 2019;144(2):377-384

Verhaak E, Schimmel WCM, Sitskoorn MM, Bakker M, Hanssens PEJ, Gehring K
PMID: 31350667 DOI: 10.1007/s11060-019-03240-w

PURPOSE: Fatigue is a common and distressing symptom in cancer patients which negatively affects patients' daily functioning and health-related quality of life. The aim of this study was to assess multidimensional fatigue in patients with brain metastases (BM) before, and after Gamma Knife radiosurgery (GKRS). **METHODS:** Patients with BM, an expected survival > 3 months, and a Karnofsky Performance Status ≥ 70 and 104 Dutch non-cancer controls were recruited. The Multidimensional Fatigue Inventory (MFI), measuring general fatigue, physical fatigue, mental fatigue, reduced activity and reduced motivation, was used. Baseline levels of fatigue between patients and controls were compared using independent-samples t-tests. The course of fatigue over time, and clinical and psychological predictors thereof, were analyzed using linear mixed models (within-group analyses). **RESULTS:** Ninety-two, 67 and 53 patients completed the MFI at baseline, and 3 and 6 months after GKRS. Before GKRS, patients with BM experienced significantly higher levels of fatigue on all subscales compared to controls (medium to large effect sizes). Over 6 months, general and physical fatigue increased significantly ($p = .009$ and $p < .001$), and levels of mental fatigue decreased significantly ($p = .027$). No significant predictors of the course of fatigue over time could be identified. **CONCLUSIONS:** Fatigue is a major problem for patients with BM. Different patterns over time were observed for the various aspects of fatigue in patients with BM. Information on the various aspects of fatigue is important because fatigue may negatively affect patients' functional independence, health-related quality of life, and adherence to therapy.

[52] Stereotactic radiosurgery in elderly patients with brain metastases: comparison with non-elderly patients using database of a multi-institutional prospective observational study (JLGK0901-Elderly).

Journal of neuro-oncology. 2019;144(2):393-402

Higuchi Y, Yamamoto M, Serizawa T, Sato Y, Shuto T, Akabane A, Jokura H, Yomo S, Nagano O, Kawagishi J, Yamanaka K, Aoyama H
PMID: 31338786 DOI: 10.1007/s11060-019-03242-8

PURPOSE: Stereotactic radiosurgery (SRS) has been increasingly used for elderly patients with brain metastases (BMs). However, no studies based on a large sample size have been reported. To compare SRS treatment results between elderly and non-elderly patients, we performed a subset study of elderly patients using our prospectively-accumulated multi-institution study database (JLGK0901 Study, *Lancet Oncol* 15:387-395, 2014). **METHODS:** During the 2009-2011 period, 1194 eligible patients undergoing gamma knife SRS alone for newly diagnosed BMs were enrolled in this study from 23 gamma knife facilities in Japan. Observation was discontinued at the end of 2013. The 1194 patients were divided into the two age groups, 693 elderly (≥ 65 years) and 501 non-elderly (< 65 years) patients. Our study protocol neither set an upper age limit nor required dose de-escalation. **RESULTS:** Median post-SRS survival time was significantly shorter in the elderly than in the non-elderly patient group (10.3 vs 14.3 months, HR 1.380, 95% CI 1.218-1.563, $p < 0.0001$). However, regarding all secondary endpoints including neurological death, neurological deterioration, SRS-related complications, leukoencephalopathy, local recurrence, newly-developed tumors, meningeal dissemination, salvage SRS, whole brain radiotherapy and surgery and decreased mini-mental state examination scores, the elderly patient group was not inferior to the non-elderly patient group. In the 693 elderly patients, there was no post-SRS median survival time difference between those with 5-10 versus 2-4 tumors (10.8 vs 8.9 months, HR 0.936, 95% CI 0.744-1.167, $p = 0.5601$). **CONCLUSIONS:** We conclude that elderly BM patients are not unfavorable candidates for SRS alone treatment.

[53] Outcome evaluation of patients treated with fractionated Gamma Knife radiosurgery for large (> 3 cm) brain metastases: a dose-escalation study.

Journal of neurosurgery. 2019;:1-10

Kim KH, Kong DS, Cho KR, Lee MH, Choi JW, Seol HJ, Kim ST, Nam DH, Lee JI
PMID: 31419791 DOI: 10.3171/2019.5.JNS19222

OBJECTIVE: Fractionated Gamma Knife radiosurgery (GKS) represents a feasible option for patients with large brain metastases (BM). However, the dose-fractionation scheme balanced between local control and radiation-induced toxicity remains unclear. Therefore, the authors conducted a dose-escalation study using fractionated GKS as the primary treatment for large (> 3 cm) BM. **METHODS:** The exclusion criteria were more than 3 lesions, evidence of leptomeningeal disease, metastatic melanoma, poor general condition, and previously treated lesions. Patients were randomized to receive 24, 27, or 30 Gy in 3 fractions (8, 9, or 10 Gy per fraction, respectively). The primary endpoint was the development of radiation necrosis assessed by a neuroradiologist blinded to the study. The secondary endpoints included the local progression-free survival (PFS) rate, change in tumor volume, development of distant intracranial progression, and overall survival. **RESULTS:** Between September 2016 and April 2018, 60 patients were eligible for the study, with 46 patients (15, 17, and 14 patients in the 8-, 9-, and 10-Gy groups, respectively) available for analysis. The median follow-up duration was 9.6 months (range 2.5-25.1 months). The 6-month estimated cumulative incidence of radiation necrosis was 0% in the 8-Gy group, 13% (95% confidence interval [CI] 0%-29%) in the 9-Gy group, and 37% (95% CI 1%-58%) in the 10-Gy group. Being in the 10-Gy group was a significant risk factor for the development of radiation necrosis ($p = 0.047$; hazard ratio [HR] 7.2, 95% CI 1.1-51.4). The 12-month local PFS rates were 65%, 80%, and 75% in the 8-, 9-, and 10-Gy groups, respectively. Being in the 8-Gy group was a risk factor for local treatment failure ($p = 0.037$; HR 2.5, 95% CI 1.1-29.6). The mean volume change from baseline was a 47.5% decrease in this cohort. Distant intracranial progression

and overall survival did not differ among the 3 groups. **CONCLUSIONS:** In this dose-escalation study, 27 Gy in 3 fractions appeared to be a relevant regimen of fractionated GKS for large BM because 30 Gy in 3 fractions resulted in unacceptable toxicities and 24 Gy in 3 fractions was associated with local treatment failure.

[54] Clinical Outcomes of Upfront Stereotactic Radiosurgery Alone for Patients With 5 to 15 Brain Metastases.

Neurosurgery. 2019;85(2):257-263

Hughes RT, McTyre ER, LeCompte M, Cramer CK, Munley MT, Laxton AW, Tatter SB, Ruiz J, Pasche B, Watabe K, Chan MD
PMID: 29982831 DOI: 10.1093/neuros/nyy276

BACKGROUND: The role of primary stereotactic radiosurgery (SRS) for patients with >4 brain metastases (BM) remains controversial. **OBJECTIVE:** To compare the outcomes of patients treated with upfront SRS alone for 1, 2 to 4, and 5 to 15 BM and assess for predictors of clinical outcomes in the 5 to 15 BM group. **METHODS:** A total of 478 patients treated with upfront SRS were stratified by number of lesions: 220 had 1 BM, 190 had 2 to 4 BM, and 68 patients had 5 to 15 BM. Overall survival and whole brain radiotherapy-free survival were estimated using the Kaplan-Meier method. The cumulative incidences of local failure and distant brain failure (DBF) were estimated using competing risks methodology. Clinicopathologic and dosimetric parameters were evaluated as predictors of survival and DBF in patients with 5 to 15 BM using Cox proportional hazards. **RESULTS:** Median overall survival was 8.0, 6.3, and 4.7 mo for patients with 1, 2 to 4, and 5 to 15 BM, respectively ($P = .14$). One-year DBF was 27%, 44%, and 40%, respectively ($P = .01$). Salvage SRS and whole brain radiotherapy rates did not differ. Progressive extracranial disease and gastrointestinal primary were associated with poor survival while RCC primary was associated with increased risk of DBF. No evaluated dose-volume parameters predicted for death, neurologic death or toxicity. **CONCLUSION:** SRS for 5 to 15 BM is well tolerated without evidence of an associated increase in toxicity, treatment failure, or salvage therapy. Further prospective, randomized studies are warranted to clarify the role of SRS for these patients.

[55] Initial SRS for Patients With 5 to 15 Brain Metastases: Results of a Multi-Institutional Experience.

International journal of radiation oncology, biology, physics. 2019;104(5):1091-1098

Hughes RT, Masters AH, McTyre ER, Farris MK, Chung C, Page BR, Kleinberg LR, Hepel J, Contessa JN, Chiang V, Ruiz J, Watabe K, Su J, Fiveash JB, Braunstein S, Chao S, Attia A, Ayala-Peacock DN, Chan MD
PMID: 30959122 DOI: 10.1016/j.ijrobp.2019.03.052

PURPOSE: Several studies evaluating stereotactic radiosurgery (SRS) for patients with >4 brain metastases (BM) demonstrated similar outcomes after treatment of 1, 2 to 4, and 5 to 15 BM; others found clinically significant survival decrements in the latter group. In this review of 8 academic centers, we compared outcomes of patients undergoing initial SRS for 1, 2 to 4, and 5 to 15 BM. **METHODS AND MATERIALS:** A total of 2089 patients treated with initial SRS for BM were included. Overall survival (OS) was estimated using the Kaplan-Meier method and compared using the log-rank test. Patient and disease characteristics were evaluated for association with OS and cumulative incidence of distant brain failure (DBF) using stepwise multivariable Cox proportional hazards and competing risk regression modeling. **RESULTS:** In this series, 989 (47%) patients had 1 metastasis, 882 (42%) had 2 to 4 metastases, and 212 (10%) had 5 to 15 metastases treated. Median OS for the 1, 2 to 4, and 5 to 15 BM groups was 14.6, 9.5, and 7.5 months, respectively (log-rank $P < .01$). Univariate and multivariable analyses revealed no difference in survival between 2 to 4 and 5 to 15 BM. DBF at 1 year was 30%, 41%, and 50%, respectively (Gray's $P < .01$). Two-year cumulative incidence of salvage SRS decreased with increasing number of BM (1: 21% vs 2-4: 19% vs 5-15: 13%; $P < .01$), but no difference in salvage whole brain radiation therapy was observed (1: 12% vs 2-4: 15% vs 5-15: 16%, $P = .10$). At the time of DBF, median brain

metastasis velocity was 3.9, 6.1, and 11.7 new metastases per year in the 1, 2 to 4, and 5 to 15 BM groups, respectively ($P < .01$). **CONCLUSIONS:** Patients treated with initial SRS for 5 to 15 BM experienced survival similar to that in patients with 2 to 4 BM. Lower rates of salvage SRS were observed in the 5 to 15 BM group, with no difference in rates of salvage whole brain radiation therapy.

[56] Primary or salvage stereotactic radiosurgery for brain metastatic small cell lung cancer.

Journal of neuro-oncology. 2019;144(1):217-225

Faramand A, Niranjan A, Kano H, Flickinger J, Lunsford LD
PMID: 31230250 DOI: 10.1007/s11060-019-03224-w

PURPOSE: We evaluated the outcomes after stereotactic radiosurgery (SRS) for patients who developed new or progressive brain disease regardless of whether they had no prior radiation, PCI, or WBRT. **METHODS:** We retrospectively identified 90 SCLC patients who had SRS between 1991 and 2018. Thirty-one patients had no evidence of brain disease at the time of initial diagnosis but received prophylactic cranial irradiation. Twenty-six without initial brain disease underwent delayed SRS after brain disease was identified. Seventeen patients with synchronous systemic and brain disease underwent WBRT at the time of diagnosis. Fifteen patients had brain disease detected at the time of initial diagnosis and had initial SRS. **RESULTS:** We found no difference in overall survival between patients who received initial PCI or WBRT compared to patients treated with SRS alone at the time when brain metastases were identified. PCI was not associated with a longer duration between initial diagnosis and the development of brain metastasis. Local tumor control was achieved in 49 out of 58 patients who had follow up MRI available for review (84.5%). Actuarial local tumor control at 3, 6, and 12 months was calculated as 92%, 85%, and 80%, respectively. Radiation therapy (PCI or WBRT) before SRS was not associated with better or worse local tumor control. **CONCLUSION:** In this experience neither prior PCI nor WBRT improved survival or local tumor control in SCLC patients who underwent SRS for new or recurrent brain disease.

[57] Stereotactic radiosurgery with and without checkpoint inhibition for patients with metastatic non-small cell lung cancer to the brain: a matched cohort study.

Journal of neurosurgery. 2019;:1-8

Shepard MJ, Xu Z, Donahue J, Eluvathingal Muttikkal TJ, Cordeiro D, Hansen L, Mohammed N, Gentzler RD, Lerner J, Fadul CE, Sheehan JP
PMID: 31349225 DOI: 10.3171/2019.4.JNS19822

OBJECTIVE: Immune checkpoint inhibitors (ICIs) improve survival in patients with advanced non-small cell lung cancer (NSCLC). Clinical trials examining the efficacy of ICIs in patients with NSCLC excluded patients with untreated brain metastases (BMs). As stereotactic radiosurgery (SRS) is commonly employed for NSCLC-BMs, the authors sought to define the safety and radiological and clinical outcomes for patients with NSCLC-BMs treated with concurrent ICI and SRS. **METHODS:** A retrospective matched cohort study was performed on patients who had undergone SRS for one or more NSCLC-derived BMs. Two matched cohorts were identified: one that received ICI before or after SRS within a 3-month period (concurrent ICI) and one that did not (ICI naive). Locoregional tumor control, peritumoral edema, and central nervous system (CNS) adverse events were compared between the two cohorts. **RESULTS:** Seventeen patients (45 BMs) and 34 patients (92 BMs) composed the concurrent-ICI and ICI-naive cohorts, respectively. There was no statistically significant difference in overall survival (HR 0.99, 95% CI 0.39-2.52, $p = 0.99$) or CNS progression-free survival (HR 2.18, 95% CI 0.72-6.62, $p = 0.11$) between the two groups. Similarly, the 12-month local tumor control rate was 84.9% for tumors in the concurrent-ICI cohort versus 76.3% for tumors in the ICI-naive cohort ($p = 0.94$). Further analysis did reveal that patients receiving concurrent ICI had increased rates of CNS complete response for BMs treated with SRS (8/16 [50%] vs 5/32 [15.6%], $p = 0.012$) per the Response Assessment in Neuro-Oncology (RANO) criteria. There was also a shorter median time to BM regression in the concurrent-ICI cohort (2.5 vs 3.1 months, $p < 0.0001$).

There was no increased rate of radiation necrosis or intratumoral hemorrhage in the patients receiving concurrent ICI (5.9% vs 2.9% in ICI-naive cohort, $p = 0.99$). There was no significant difference in the rate of peritumoral edema progression between the two groups (concurrent ICI: 11.1%, ICI naive: 21.7%, $p = 0.162$).

CONCLUSIONS: The concurrent use of ICI and SRS to treat NSCLC-BM was well tolerated while providing more rapid BM regression. Concurrent ICI did not increase peritumoral edema or rates of radiation necrosis. Further studies are needed to evaluate whether combined ICI and SRS improves progression-free survival and overall survival for patients with metastatic NSCLC.

[58] Preoperative Dural Contact and Recurrence Risk After Surgical Cavity Stereotactic Radiosurgery for Brain Metastases: New Evidence in Support of Consensus Guidelines.

Advances in radiation oncology. 2019;4(3):458-465

Susko M, Yu Y, Ma L, Nakamura J, Fogh S, Raleigh DR, Golden E, Theodosopoulos PV, McDermott MW, Sneed PK, Braunstein SE
PMID: 31360800 DOI: 10.1016/j.adro.2019.03.002

PURPOSE: The incidence of brain metastases is increasing as a result of more routine diagnostic imaging and improved extracranial systemic treatment strategies. As noted in recent consensus guidelines, postoperative stereotactic radiosurgery (SRS) to the resection cavity has lower rates of local control than whole brain radiation therapy but improved cognitive outcomes. Further analyses are needed to improve local control and minimize toxicity. **METHODS AND MATERIALS:** Patients receiving SRS to a resection cavity between 2006 and 2016 were retrospectively analyzed. Presurgical variables, including tumor location, diameter, dural/meningeal contact, and histology, were collected, as were SRS treatment parameters. Patients had routine follow-up with magnetic resonance imaging, and those noted to have local failure were further assessed for the recurrence location, distance from the target volume, and dosimetric characteristics. **RESULTS:** Overall, 82 patients and 85 resection cavities underwent postoperative SRS during the study period. Of these, 58 patients with 60 resection cavities with available follow-up magnetic resonance imaging scans were included in this analysis. With a median follow-up of 19.8 months, local recurrence occurred in 12 of the resection cavities for a 15% 1-year and 18% 2-year local recurrence rate. Pretreatment tumor volume contacted the dura/meninges in 100% of cavities with recurrence versus 67% of controlled cavities ($P = .025$). A total of 5 infield, 5 marginal, and 4 out-of-field recurrences were found, with a median distance to the centroid from the target volume of 3 mm. The addition of a 10-mm dural margin increased the target volume overlap with the recurrence contours for 10 of the 14 recurrences. **CONCLUSIONS:** Dural contact was associated with an increased rate of recurrence for patients who received SRS to a surgical cavity, and the median distance of marginal recurrences from the target volume was 3 mm. These results provide evidence in support of recent consensus guidelines suggesting that additional dural margin on SRS volumes may benefit local control.

[59] Health-related quality of life of patients with brain metastases selected for stereotactic radiosurgery.

Journal of neuro-oncology. 2019;143(3):537-546

Verhaak E, Gehring K, Hanssens PEJ, Sitskoorn MM
PMID: 31073966 DOI: 10.1007/s11060-019-03186-z

PURPOSE: Information on health-related quality of life (HRQoL) of patients with brain metastases (BM) before stereotactic radiosurgery (SRS) is very relevant to improve communication between patients and clinicians and to be able to interpret changes in HRQoL after SRS. The aim of this study was to evaluate the prevalence and severity of complaints on different aspects of pre-SRS HRQoL among patients with BM and to identify predictors thereof. **METHODS:** Patients with 1-10 newly diagnosed BM, expected survival > 3 months, Karnofsky Performance Status ≥ 70 , and scheduled to undergo SRS were included. HRQoL was measured with the Functional Assessment of Cancer Therapy-Brain (FACT-Br) questionnaire. One-sample z-tests were conducted to analyze differences between patients with BM and published normative data of a general adult

sample and of an adult cancer sample. Multiple regression analyses were run to identify predictors of pre-SRS HRQoL. **RESULTS:** On the individual level, most patients with BM (57.6% of 92 included patients) reported complaints regarding emotional well-being. As a group, patients with BM reported significantly lower emotional well-being compared to both control groups and significantly higher social well-being compared to the general population. Worse psychological factors, e.g. physical fatigue, depression, mental fatigue and anxiety, predicted aspects of pre-SRS HRQoL. **CONCLUSIONS:** An increased understanding of pre-SRS HRQoL and predictors hereof, provides us with more insight into the well-being of our patients with BM and is necessary for the interpretation of (changes in) HRQoL after SRS.

[60] Combination of Trastuzumab Emtansine and Stereotactic Radiosurgery Results in High Rates of Clinically Significant Radionecrosis and Dysregulation of Aquaporin-4.

Clinical cancer research : an official journal of the American Association for Cancer Research. 2019;25(13):3946-3953

Stumpf PK, Cittelly DM, Robin TP, Carlson JA, Stuhr KA, Contreras-Zarate MJ, Lai S, Ormond DR, Rusthoven CG, Gaspar LE, Rabinovitch R, Kavanagh BD, Liu A, Diamond JR, Kabos P, Fisher CM

PMID: 30940654 DOI: 10.1158/1078-0432.CCR-18-2851

PURPOSE: Patients with human EGFR2-positive (HER2(+)) breast cancer have a high incidence of brain metastases, and trastuzumab emtansine (T-DM1) is often employed. Stereotactic radiosurgery (SRS) is frequently utilized, and case series report increased toxicity with combination SRS and T-DM1. We provide an update of our experience of T-DM1 and SRS evaluating risk of clinically significant radionecrosis (CSRN) and propose a mechanism for this toxicity. **EXPERIMENTAL DESIGN:** Patients with breast cancer who were \leq 45 years regardless of HER2 status or had HER2(+) disease regardless of age and underwent SRS for brain metastases were included. Rates of CSRN, SRS data, and details of T-DM1 administration were recorded. Proliferation and astrocytic swelling studies were performed to elucidate mechanisms of toxicity. **RESULTS:** A total of 45 patients were identified; 66.7% were HER2(+), and 60.0% were \leq 45 years old. Of the entire cohort, 10 patients (22.2%) developed CSRN, 9 of whom received T-DM1. CSRN was observed in 39.1% of patients who received T-DM1 versus 4.5% of patients who did not. Receipt of T-DM1 was associated with a 13.5-fold ($P = 0.02$) increase in CSRN. Mechanistically, T-DM1 targeted reactive astrocytes and increased radiation-induced cytotoxicity and astrocytic swelling via upregulation of Aquaporin-4 (Aqp4). **CONCLUSIONS:** The strong correlation between development of CSRN after SRS and T-DM1 warrants prospective studies controlling for variations in timing of T-DM1 and radiation dosing to further stratify risk of CSRN and mitigate toxicity. Until such studies are completed, we advise caution in the combination of SRS and T-DM1.

[61] Applicability and limitations of a recently-proposed prognostic grading metric, initial brain metastasis velocity, for brain metastasis patients undergoing stereotactic radiosurgery.

Journal of neuro-oncology. 2019;143(3):613-621

Yamamoto M, Aiyama H, Koiso T, Watanabe S, Kawabe T, Sato Y, Higuchi Y, Kasuya H, Barford BE

PMID: 31140039 DOI: 10.1007/s11060-019-03199-8

PURPOSE: This study, based on our brain metastasis (BM) patients undergoing stereotactic radiosurgery (SRS) procedures, aimed to validate whether the recently-proposed prognostic grading system, initial brain metastasis velocity (iBMV, scoring the cumulative number of BMs at the time of SRS divided by time [years] since the initial primary cancer diagnosis), is generally applicable.

METHODS: This was an institutional review board-approved, retrospective cohort study using our prospectively accumulated database including 3498 patients who underwent SRS for BMs during the 19.5-year-period between July, 1998 and December, 2017. We excluded four lost to follow-up, 24 for whom the day of primary cancer diagnosis was not available, 665 with synchronous presentation

and 651 with pre-SRS radiotherapy and/or surgery, ultimately studying 2150 patients. Patients were categorized into two classes by iBMV scores, i.e., < 2.00 and ≥ 2.00 . **RESULTS:** In a multivariable model, iBMV was directly associated with a higher risk of death ($p < 0.0001$). The median survival time of patients with iBMV scores < 2.00 , 10.0 (95% CI; 9.2-10.9) months, was longer than that of patients with iBMV scores ≥ 2.00 , 6.3 (5.6-6.7) months, showing a significant difference between the two groups (HR 1.599, 95% CI 1.458-1.753, $p < 0.0001$). The same results were obtained in patients with non-small cell lung, breast, kidney or other cancers. Among 608 patients who underwent repeat SRS for newly-developed BMs, iBMV score categories correlated well with brain metastasis velocity risk groups ($p < 0.0001$). **CONCLUSIONS:** Our present results support the validity of iBMV for predicting survival after SRS.

[62] The case for radiosurgery for brainstem metastases.

Journal of neuro-oncology. 2019;143(3):585-595

Winograd E, Rivers CI, Fenstermaker R, Fabiano A, Plunkett R, Prasad D

PMID: 31127508 DOI: 10.1007/s11060-019-03195-y

PURPOSE: To challenge the prevalent pessimism regarding the outcome of patients with metastases in the brainstem resulting in the use of whole brain radiation for palliation rather than stereotactic radiosurgery for definitive control and preservation of quality of life. We present our single institution review of the efficacy and safety of treating brainstem metastases aggressively with GKRS.

METHODS: Forty-one patients with 45 total lesions treated with GKRS were included. Mean age was 58.7 years, ranging from 22 to 82. Tumor volumes were objectively calculated, treatment effects assessed on imaging and clinical data collected and correlated to the radiosurgical response. **RESULTS:** Mean survival after diagnosis of BSM was 11.6 months, ranging from 1.4 to 58.8 months. Margin dose ranged from 12 to 20 Gy. At first follow up, 11 (27%) patients had complete resolution of the treated lesion. At the second follow up 15 (37%) and third follow up 19 (46%) patients had a complete response. On average, there was a 64% decrease in tumor size at first follow up after treatment. 25 (61%) patients received WBRT in addition to radiosurgery; 16 (39%) received radiosurgery alone. There was no difference in overall survival between the two groups ($p = 0.1324$). ARE was seen in one patient who received 16 Gy to the margin of a 2.06 cm(3) pontine tumor, but without correlative symptoms. One patient was treated with Bevacizumab(R) for progressive, but asymptomatic, edema following treatment that was not controlled by corticosteroids. **CONCLUSIONS:** Location in brainstem should not be a deterrent to the use of radiosurgery for these patients. The addition or exclusion of WBRT should be based on the clinical progression of the patient and within the limits of this study does not seem to impact overall survival. With improved survival as a result of better systemic therapy, these patients can benefit from better preservation of cognitive function by this strategy.

[63] Tumor Cavity Recurrence after Stereotactic Radiosurgery of Surgically Resected Brain Metastases: Implication of Deviations from Contouring Guidelines.

Stereotactic and functional neurosurgery. 2019;97(1):24-30

McDermott DM, Hack JD, Cifarelli CP, Vargo JA

PMID: 30763944 DOI: 10.1159/000496156

BACKGROUND: Significant heterogeneity exists in target volumes for postoperative stereotactic radiosurgery (SRS) for brain metastases. A set of contouring guidelines was recently published, and we investigated the impact of deviations. **METHODS:** Patients ($n = 41$) undergoing single-fraction Gamma Knife SRS following surgical resection of brain metastases from 2011 to 2017 were retrospectively reviewed. SRS included the entire contrast-enhancing cavity with heterogeneity in inclusion of the surgical tract and no routine margin along the dura or clinical target volume margin. Follow-up MR imaging was fused with SRS plans to assess patterns of failure. **RESULTS:** The median follow-up was 11.1 months with a median prescription of 18 Gy. There were 5 local failures: infield ($n = 3$, 60%), surgical tract ($n = 1$, 20%), and marginal > 5 mm from the resection cavity ($n = 1$, 20%). No marginal failures < 5 mm or dural margin failures were

noted. For deep lesions (n = 13), 62% (n = 8) had the entire tract covered. The only tract recurrence was in a deep lesion without coverage of the surgical tract (n = 1/5). **CONCLUSION:** In this small preliminary experience, despite no routine inclusion of the dural tract or bone flap, no failures were noted in these locations. Omission of the surgical tract in deep lesions may increase failure rates.

[64] Single-Session versus Multisession Gamma Knife Radiosurgery for Large Brain Metastases from Non-Small Cell Lung Cancer: A Retrospective Analysis.

Stereotactic and functional neurosurgery. 2019;97(2):94-100

Park K, Kim JW, Chung HT, Paek SH, Kim DG

PMID: 31117101 DOI: 10.1159/000496154

PURPOSE: To evaluate the efficacy of Gamma Knife radiosurgery (GKS) in patients with large brain metastases by comparing single-session radiosurgery (S-GKS) and multisession radiosurgery (M-GKS), we retrospectively analyzed the clinical outcomes of patients who underwent GKS for brain metastases from non-small cell lung cancer (NSCLC). **MATERIALS AND METHODS:** Between January 2010 and December 2016, 66 patients with 74 lesions ≥ 10 cm³ from large brain metastases from only NSCLC were included. Fifty-five patients with 60 lesions were treated with S-GKS; 11 patients with 14 lesions were treated with M-GKS. Median doses were 16 Gy (range, 11-18 Gy) for the S-GKS group and 8 Gy (range, 7-10 Gy) in three fractions for the M-GKS group. **RESULTS:** With a mean follow-up period of 13.1 months (range, 1.3-76.4 months), the median survival duration was 21.1 months for all patients. Median tumor volume was 14.3 cm³ (range, 10.0-58.3 cm³). The local control rate was 77.0% and the progression-free survival rate was 73.6% at the last follow-up. There were no significant between-group differences in terms of local control rate (p = 0.10). Compared with S-GKS, M-GKS did not differ significantly in radiation-induced complications (38.1 vs. 45.4%, p = 0.83). While 8 patients who underwent S-GKS experienced major complications of grade ≥ 3 , no toxicity was observed in patients treated with M-GKS. **CONCLUSIONS:** M-GKS may be an effective alternative for large brain metastases from NSCLC. Specifically, severe radiation-induced toxicity (\geq grade 3) did not occur in M-GKS for large-volume metastases. Although the long-term effects and results from larger samples remain unclear, M-GKS may be a suitable palliative treatment for preserving neurological function.

[65] Stereotactic radiosurgery for the treatment of brain metastasis from gastrointestinal primary cancers.

Journal of radiosurgery and SBRT. 2019;6(1):27-34

Paudel N, Helenowski I, Kane L, Sachdev S, Bloch O, Tate M, Chandler JP, Kruser TJ
PMID: 30775072 DOI:

PURPOSE: We aimed to determine the efficacy of gamma knife stereotactic radiosurgery (SRS) to control brain metastases (BM) from GI primaries and report on the patient outcomes. **MATERIALS/METHODS:** We retrospectively evaluated patients who had undergone SRS at our institution for the treatment BM from GI primaries from 2000 to 2016. Actuarial rates for overall survival (OS) and local control (LC) were calculated. Survival rates were computed via the Kaplan-Meier method from the day of SRS. Multivariate analysis (MVA) using proportional hazards regression was done to determine prognostic factors for OS and LC. **RESULTS:** 53 patients with a total of 148 BM were treated with SRS. The median age at SRS was 60 years and the median treatment dose was 18 Gy. SRS was given as an adjuvant treatment to 30.4% of lesions. Twelve patients underwent second course of SRS for new/recurrent lesions at a median of 8 months from the first SRS (range 2-25.5). Twelve patients (22.6%) received salvage whole brain radiation. The median follow up time from the diagnosis of BM was 6 months. Local control rate at 6 months was 74.33% and 57.21% at 12 months. The OS at 1 year was 34% and 8% at 3 years. On MVA, higher GK dose was associated with better LC, and >10 BM trended towards higher risk of local recurrence (LR). None of the tested factors proved to be significant for OS on MVA. No radiographic radionecrosis was observed on follow up MRI. **CONCLUSIONS:** SRS is a safe treatment modality for the management of CNS metastases from GI primary. Consideration for dose-escalated approaches may improve LC rates.

[66] Stereotactic Radiosurgery for Patients with 10 or More Brain Metastases.

Progress in neurological surgery. 2019;34:110-124

Yamamoto M, Higuchi Y, Sato Y, Aiyama H, Kasuya H, Barford BE

PMID: 31096244 DOI: 10.1159/000493056

The JLKG0901 study showed the non-inferiority of stereotactic radiosurgery (SRS) alone as the initial treatment for 5-10 as compared to 2-4 brain metastases (BM) in terms of overall survival and most secondary endpoints [Lancet Oncol 2014;15:387-395]. A trend for patients with 5-10 tumors to undergo SRS alone has since become apparent. The next step is to reappraise whether results of SRS treatment alone for tumor numbers ≥ 10 differ from those for 2-9 tumors. During the past 2 decades, several retrospective studies have demonstrated the SRS alone treatment strategy to have certain benefits for carefully selected patients with ≥ 10 BM, i.e., a sufficiently long survival period with lower incidences of neurological death, neurological deterioration, local recurrence, and SRS-related complications. Herein, we introduce our Mito experiences with SRS for ≥ 10 BM, employing a case-matched study on 934 patients, 467 each in groups with 2-9 BM and ≥ 10 BM. Post-SRS treatment results, i.e., median survival time, neurological death-free survival time and cumulative incidences of local recurrence, repeat SRS for new lesions, neurological deterioration, and SRS-related complications, were not inferior for patients with ≥ 10 BM as compared to those with 2-9 BM. We conclude that patients with ≥ 10 tumors are not unfavorable candidates for SRS alone.

[67] Epidermal growth factor receptor mutations: association with favorable local tumor control following Gamma Knife radiosurgery in patients with non-small cell lung cancer and brain metastases.

Journal of neurosurgery. 2019;:1-8

Lee CC, Hsu SPC, Lin CJ, Wu HM, Chen YW, Luo YH, Chiang CL, Hu YS, Chung

WY, Shiau CY, Guo WY, Hung-Chi Pan D, Yang HC

PMID: 31226692 DOI: 10.3171/2019.4.JNS19446

OBJECTIVE: The presence of epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer (NSCLC) has been associated with elevated radiosensitivity in vitro. However, results from clinical studies on radiosensitivity in cases of NSCLC with EGFR mutations are inconclusive. This paper presents a retrospective analysis of patients with NSCLC who underwent regular follow-up imaging after radiotherapy for brain metastases (BMs). The authors also investigated the influence of EGFR mutations on the efficacy of Gamma Knife radiosurgery (GKRS). **METHODS:** This study included 264 patients (1069 BMs) who underwent GKRS treatment and for whom EGFR mutation status, demographics, performance status, and tumor characteristics were available. Radiological images were obtained at 3 months after GKRS and at 3-month intervals thereafter. Kaplan-Meier plots and Cox regression analysis were used to correlate EGFR mutation status and other clinical features with tumor control and overall survival. **RESULTS:** The tumor control rates and overall 12-month survival rates were 87.8% and 65.5%, respectively. Tumor control rates in the EGFR mutant group versus the EGFR wild-type group were 90.5% versus 79.4% at 12 months and 75.0% versus 24.5% at 24 months. During the 2-year follow-up period after SRS, the intracranial response rate in the EGFR mutant group was approximately 3-fold higher than that in the wild-type group (p < 0.001). Cox regression multivariate analysis identified EGFR mutation status, extracranial metastasis, primary tumor control, and prescribed margin dose as predictors of tumor control (p = 0.004, p < 0.001, p = 0.004, and p = 0.026, respectively). Treatment with a combination of GKRS and tyrosine kinase inhibitors (TKIs) was the most important predictor of overall survival (p < 0.001). **CONCLUSIONS:** The current study demonstrated that, among patients with NSCLC-BMs, EGFR mutations were independent prognostic factors of tumor control. It was also determined that a combination of GKRS and TKI had the most pronounced effect on prolonging survival after SRS. In select patient groups, treatment with SRS in conjunction with EGFR-TKIs provided effective tumor control for NSCLC-BMs.

[68] Lymphopenia predicts response to stereotactic radiosurgery in lung cancer patients with brain metastases.

Journal of neuro-oncology. 2019;143(2):337-347

Li YD, Lamano JB, Kaur G, Lamano JB, Veliceasa D, Biyashev D, Kruser T, Bloch O
PMID: 30982197 DOI: 10.1007/s11060-019-03169-0

BACKGROUND: Stereotactic radiosurgery (SRS) can enhance immune activation and improve disease control through stimulation of anti-tumor immunity. However, patients with cancer receiving chemotherapy are often immunosuppressed, which may impact the efficacy of SRS. Here we investigate the relationship between systemic lymphopenia and response to SRS in patients with brain-metastatic lung cancer. **METHODS:** We reviewed 125 patients with lung cancer brain metastases treated with SRS between January 2014 and May 2017. Complete blood counts from the time of SRS were reviewed, and lymphopenia was defined as absolute lymphocyte count $< 1 \times 10^9$ cells/L. Kaplan-Meier survival analysis and cox proportional-hazards models were used to evaluate risks of progression and death. **RESULTS:** The median age was 65 years (range 43-86), with 54% female patients. Lymphopenia was present in 60 patients. In univariate analysis, lymphopenic patients had significantly shorter PFS (HR = 2.995, $p < 0.0001$) and OS (HR = 3.928, $p < 0.0001$). When accounting for age, gender, smoking history, ECOG score, surgery, and tumor histology in a multivariate model, lymphopenia remained significantly predictive of worse PFS (HR = 1.912, $p = 0.002$) and OS (HR = 2.257, $p < 0.001$). Patients who received immunotherapy within 3 months of SRS demonstrated significantly shorter PFS (HR = 3.578, $p = 0.006$) and OS (HR = 6.409, $p = 0.001$) if lymphopenic. **CONCLUSIONS:** Brain-metastatic lung cancer patients with lymphopenia treated with SRS had significantly worse PFS and OS. The effect of lymphopenia was even more pronounced in patients receiving immunotherapy. These data demonstrate the significant impact of deficient immunity on disease control and survival. Lymphopenic patients may benefit from interventions to improve immune function prior to SRS for brain metastases.

[69] Gamma Knife Radiosurgery for the Management of More Than 15 Cerebral Metastases.

World neurosurgery. 2019;126:e989-e997

Bowden G, Faramand A, Niranjan A, Lunsford LD, Monaco E 3rd

PMID: 30876993 DOI: 10.1016/j.wneu.2019.03.019

BACKGROUND: The number of metastases that can be treated safely and effectively with Gamma Knife stereotactic radiosurgery (SRS) remains controversial despite continuing evidence to support its expanded utilization. We endeavored to elucidate the survival outcomes for patients who presented with ≥ 15 brain metastases at the time of initial SRS. **METHODS:** This retrospective analysis reviewed patients treated for ≥ 15 brain metastases originating from breast cancer, lung cancer, or melanoma. Ninety-three patients met the inclusion criteria. In this study, 3016 tumors were treated. The median number of tumors at the first SRS procedure was 23 (range, 15-67) for breast cancer, 21 (range, 15-48) for lung cancer, and 21 (range, 15-67) for melanoma. The mean aggregate metastases volume was 8.75 cm³ for breast, 6.89 cm³ for lung, and 9.98 cm³ for melanoma. **RESULTS:** Patients with breast cancer, lung cancer, and melanoma had a median survival after diagnosis of brain metastases of 18.0, 9.4, and 6.3 months, respectively. The survival after SRS was 16 months for breast cancer, 4.6 months for lung cancer, and 3.1 months for melanoma. Patients with breast cancer had significantly longer survival than patients with lung cancer and melanoma after SRS ($P = 0.001$). A higher Karnofsky Performance Status score was associated with an increase in survival across all tumor types. Repeat SRS for local or distant progression was performed in 56% of patients with breast cancer, 35% of patients with lung cancer, and 24% of patients with melanoma. **CONCLUSIONS:** SRS is an effective means of managing extensive brain metastases, particularly in patients with breast cancer. The primary tumor type, systemic disease, and performance status heavily influence survival outcomes.

[70] Survival and prognostic factors in patients with gastrointestinal cancers and brain metastases: have we made progress?

Translational research : the journal of laboratory and clinical medicine.

2019;208:63-72

Sperduto PW, Fang P, Li J, Breen W, Brown PD, Cagney D, Aizer A, Yu J, Chiang V, Jain S, Gaspar LE, Myrehaug S, Sahgal A, Braunstein S, Sneed P, Cameron B, Attia A, Molitoris J, Wu CC, Wang TJC, Lockney N, Beal K, Parkhurst J, Buatti JM, Shanley R, Lou E, Tandberg DD, Kirkpatrick JP, Shi D, Shih HA, Chuong M, Saito H, Aoyama H, Masucci L, Roberge D, Mehta MP

PMID: 30885538 DOI: 10.1016/j.trsl.2019.02.011

The literature describing the prognosis of patients with gastrointestinal (GI) cancers and brain metastases (BM) is sparse. Our group previously published a prognostic index, the Graded Prognostic Assessment (GPA) for GI cancer patients with BM, based on 209 patients diagnosed from 1985-2005. The purpose of this analysis is to identify prognostic factors for GI cancer patients with newly diagnosed BM in a larger contemporary cohort. A multi-institutional retrospective IRB-approved database of 792 GI cancer patients with new BM diagnosed from 1/1/2006 to 12/31/2016 was created. Demographic data, clinical parameters, and treatment were correlated with survival and time from primary diagnosis to BM (TPDBM). Kaplan-Meier median survival (MS) estimates were calculated and compared with log-rank tests. The MS from time of first treatment for BM for the prior and current cohorts were 5 and 8 months, respectively ($P < 0.001$). Eight prognostic factors (age, stage, primary site, resection of primary tumor, Karnofsky Performance Status (KPS), extracranial metastases, number of BM and Hgb) were found to be significant for survival, in contrast to only one (KPS) in the prior cohort. In this cohort, the most common primary sites were rectum (24%) and esophagus (23%). Median TPDBM was 22 months. Notably, 37% (267/716) presented with poor prognosis (GPA 0-1.0). Although little improvement in overall survival in this cohort has been achieved in recent decades, survival varies widely and multiple new prognostic factors were identified. Future work will translate these factors into a prognostic index to facilitate clinical decision-making and stratification of future clinical trials.

[71] Volumetric changes of intracranial metastases during the course of fractionated stereotactic radiosurgery and significance of adaptive planning.

Journal of neurosurgery. 2019;:1-6

Lee MH, Kim KH, Cho KR, Choi JW, Kong DS, Seol HJ, Nam DH, Lee JI

PMID: 31151111 DOI: 10.3171/2019.3.JNS183130

OBJECTIVE: Fractionated Gamma Knife surgery (FGKS) has recently been used to treat large brain metastases. However, little is known about specific volume changes of lesions during the course of treatment. The authors investigated short-term volume changes of metastatic lesions during FGKS. **METHODS:** The authors analyzed 33 patients with 40 lesions who underwent FGKS for intracranial metastases of non-small-cell lung cancer (NSCLC; 25 patients with 32 lesions) and breast cancer (8 patients with 8 lesions). FGKS was performed in 3-5 fractions. Baseline MRI was performed before the first fraction. MRI was repeated after 1 or 2 fractions. Adaptive planning was executed based on new images. The median prescription dose was 8 Gy (range 6-10 Gy) with a 50% isodose line. **RESULTS:** On follow-up MRI, 18 of 40 lesions (45.0%) showed decreased tumor volumes (TVs). A significant difference was observed between baseline (median 15.8 cm³) and follow-up (median 14.2 cm³) volumes ($p < 0.001$). A conformity index was significantly decreased when it was assumed that adaptive planning was not implemented, from baseline (mean 0.96) to follow-up (mean 0.90, $p < 0.001$). The average reduction rate was 1.5% per day. The median follow-up duration was 29.5 weeks (range 9-94 weeks). During the follow-up period, local recurrence occurred in 5 lesions. **CONCLUSIONS:** The TV showed changes with a high dose of radiation during the course of FGKS. Volumetric change caused a significant difference in the clinical parameters. It is expected that adaptive planning would be helpful in the case of radiosensitive tumors such as NSCLCs or breast cancer to ensure an adequate dose to the target area and reduce unnecessary exposure of normal tissue to radiation.

[72] Stereotactic radiosurgery with concurrent HER2-directed therapy is associated with improved objective response for breast cancer brain metastasis. *Neuro-oncology*. 2019;21(5):659-668

Kim JM, Miller JA, Kotecha R, Chao ST, Ahluwalia MS, Peereboom DM, Mohammadi AM, Barnett GH, Murphy ES, Vogelbaum MA, Angelov L, Abraham J, Moore H, Budd GT, Suh JH

PMID: 30726965 DOI: 10.1093/neuonc/noz006

BACKGROUND: Patients with breast cancer positive for human epidermal growth factor receptor 2 (HER2) remain at high risk of intracranial relapse following treatment and experience increased rates of intracranial failure after stereotactic radiosurgery (SRS). We hypothesized that the addition of concurrent lapatinib to SRS would improve intracranial complete response rates. **METHODS:** Patients with newly diagnosed HER2-amplified breast cancer brain metastases from 2005-2014 who underwent SRS were included and divided into 2 cohorts based on timing of treatment with lapatinib. Outcome variables included the proportion of patients who achieved an intracranial complete response or progressive disease according to the RECIST 1.1 criteria, as well as individual lesion response rates, distant intracranial failure, and radiation necrosis. **RESULTS:** Eighty-four patients with 487 brain metastases met inclusion criteria during the study period. Over 138 treatment sessions, 132 lesions (27%) were treated with SRS and concurrent lapatinib, while 355 (73%) were treated with SRS without lapatinib. Compared with patients treated with SRS alone, patients treated with concurrent lapatinib had higher rates of complete response (35% vs 11%, $P = 0.008$). On a per-lesion basis, best objective response was superior in the concurrent lapatinib group (median 100% vs 70% reduction, $P < 0.001$). Concurrent lapatinib was not associated with an increased risk of grade 2+ radiation necrosis (1.0% with concurrent lapatinib vs 3.5% without, $P = 0.27$). Lapatinib had no protective effect on distant intracranial failure rates (48% vs 49%, $P = 0.91$). **CONCLUSION:** The addition of concurrent lapatinib to SRS was associated with improved complete response rates among patients with HER2-positive brain metastases.

[73] Salvage Stereotactic Radiosurgery in Breast Cancer Patients with Multiple Brain Metastases.

World neurosurgery. 2019;125:e479-e486

Perez JL, Ozpinar A, Kano H, Phan B, Niranjana A, Lunsford LD

PMID: 30710716 DOI: 10.1016/j.wneu.2019.01.108

BACKGROUND: The overall survival rates for breast cancer are increasing due to controlled brain disease and improved systemic treatments. This study examined neurologic outcomes, tumor control, and survival data in breast cancer patients with multiple brain metastases and who required salvage stereotactic radiosurgery (SRS) for recurrent breast cancer brain metastases. **METHODS:** The study included 231 patients with a primary diagnosis of breast cancer who underwent SRS for more than 1 brain metastases from May 1993 and July 2007. Survival analyses via univariate and multivariate Cox regression demonstrated interactions between survival and predictor values including Karnofsky Performance Scale, Recursive Partitioning Analysis Class, number of brain metastases, whole-brain radiotherapy (WBRT), immunotherapy, and chemotherapy. **RESULTS:** Of the 231 patients, the survival rate was 53% at 1 year and 26% at 5 years from initial SRS. Controlled systemic disease, adjuvant chemotherapy, and Recursive Partitioning Analysis class II were significant predictors of increased survival, while WBRT was a significant predictor of decreased survival. The median survival in patients who received WBRT after SRS was 11 months versus 23 months in those who did not. The local tumor control rate at initial follow-up was 95%. Of these, 40% of patients underwent additional brain SRS. Following salvage SRS, 8% of patients developed symptomatic adverse radiation events; however, the development of symptomatic adverse radiation events had no effect on patient survival. **CONCLUSIONS:** This report indicated that both initial and salvage SRS procedures in breast cancer patients with multiple brain metastases are effective for local control of intracranial disease while minimizing adverse radiation effects.

[74] Comparison between stereotactic radiosurgery and whole-brain radiotherapy for 10-20 brain metastases from non-small cell lung cancer.

Molecular and clinical oncology. 2019;10(5):560-566

Mizuno T, Takada K, Hasegawa T, Yoshida T, Murotani K, Kobayashi H, Sakurai T, Yamashita Y, Akazawa N, Kojima E

PMID: 30967951 DOI: 10.3892/mco.2019.1830

The efficacy and safety of stereotactic radiosurgery (SRS) in comparison with whole brain radiotherapy (WBRT) for brain metastases (BMs) remains unclear. The present study retrospectively reviewed 44 patients who received SRS or WBRT as an initial treatment for 10-20 BMs from non-small cell lung cancer between 2009 and 2016. Of the patients, 24 (54.5%) were treated with SRS and 20 (45.5%) were treated with WBRT. Overall survival (OS), time to intracranial progression (TTIP), neurological survival (NS), and prognostic factors were examined. OS did not significantly differ between the two groups: 7.3 months in the SRS group vs. 7.2 months in the WBRT group ($P=0.502$). Median TTIP was significantly shorter in the SRS group than in the WBRT group (7.1 vs. 19.1 months, $P=0.009$). In contrast, there were no significant differences in NS between the two groups (14.5 months in the SRS group vs. 12.9 months in the WBRT group, $P=0.346$). Univariate and multivariate analysis revealed that the type of initial treatment for BMs (WBRT or SRS) was not a significant prognostic factor (hazard ratio=0.80, 95% confidence interval: 0.42-1.52, $P=0.502$). However, histology, performance status, subsequent molecular targeted drugs, subsequent chemotherapy and salvage treatment were independent prognostic factors. There were no significant differences in OS and NS between treatment with SRS and treatment with WBRT in patients with 10-20 BMs, although TTIP was improved with WBRT. As an upfront treatment for 10-20 BMs, SRS may delay WBRT and the adverse events associated with WBRT.

[75] Local tumor progression treated with Gamma Knife radiosurgery: differences between patients with 2-4 versus 5-10 brain metastases based on an update of a multi-institutional prospective observational study (JLGK0901).

Journal of neurosurgery. 2019;:1-10

Serizawa T, Yamamoto M, Higuchi Y, Sato Y, Shuto T, Akabane A, Jokura H, Yomo S, Nagano O, Kawagishi J, Yamanaka K

PMID: 31026833 DOI: 10.3171/2019.1.JNS183085

OBJECTIVE: The Japanese Leksell Gamma Knife (JLGK)0901 study proved the efficacy of Gamma Knife radiosurgery (GKRS) in patients with 5-10 brain metastases (BMs) as compared to those with 2-4, showing noninferiority in overall survival and other secondary endpoints. However, the difference in local tumor progression between patients with 2-4 and those with 5-10 BMs has not been sufficiently examined for this data set. Thus, the authors reappraised this issue, employing the updated JLGK0901 data set with detailed observation via enhanced MRI. They applied sophisticated statistical methods to analyze the data. **METHODS:** This was a prospective observational study of 1194 patients harboring 1-10 BMs treated with GKRS alone. Patients were categorized into groups A (single BM, 455 cases), B (2-4 BMs, 531 cases), and C (5-10 BMs, 208 cases). Local tumor progression was defined as a 20% increase in the maximum diameter of the enhanced lesion as compared to its smallest documented maximum diameter on enhanced MRI. The authors compared cumulative incidence differences determined by competing risk analysis and also conducted propensity score matching. **RESULTS:** Local tumor progression was observed in 212 patients (17.8% overall, groups A/B/C: 93/89/30 patients). Cumulative incidences of local tumor progression in groups A, B, and C were 15.2%, 10.6%, and 8.7% at 1 year after GKRS; 20.1%, 16.9%, and 13.5% at 3 years; and 21.4%, 17.4%, and not available at 5 years, respectively. There were no significant differences in local tumor progression between groups B and C. Local tumor progression was classified as tumor recurrence in 139 patients (groups A/B/C: 68/53/18 patients), radiation necrosis in 67 (24/31/12), and mixed/undetermined lesions in 6 (1/5/0). There were no significant differences in tumor recurrence or radiation necrosis between groups B and C. Multivariate analysis using the Fine-Gray proportional hazards model revealed age < 65 years, neurological symptoms, tumor volume ≥ 1 cm³, and prescription dose < 22 Gy to be significant poor prognostic

factors for local tumor progression. In the subset of 558 case-matched patients (186 in each group), there were no significant differences between groups B and C in local tumor progression, nor in tumor recurrence or radiation necrosis. **CONCLUSIONS:** Local tumor progression incidences did not differ between groups B and C. This study proved that tumor progression after GKRS without whole-brain radiation therapy for patients with 5-10 BMs was satisfactorily treated with the doses prescribed according to the JLGK0901 study protocol and that results were not inferior to those in patients with a single or 2-4 BMs. Clinical trial registration no.: UMIN000001812 (umin.ac.jp).

[76] Volume not number of metastases: Gamma Knife radiosurgery management of intracranial lesions from an Australian perspective.

Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2019;133:43-49

Izard MA, Moutrie V, Rogers JM, Beath K, Grace M, Karle B, Ho A, Fuller JW
PMID: 30935580 DOI: 10.1016/j.radonc.2018.12.018

BACKGROUND AND PURPOSE: To assess the response of the first cohort of patients treated with Gamma Knife radiosurgery in Australia. **MATERIALS AND METHODS:** A prospectively collected cohort of 180 patients with intracranial metastases from different primaries was treated between August 2010 and July 2017. Survival was calculated using the Kaplan-Meier's method. Cox regression was used for multivariate analysis. **RESULTS:** Currently 141 patients (78.3%) have died of their disease. The median survival for the group as a whole was 9.2 months, with observed differences resulting from the volume of tumor burden (11.4 months for volumes <3.2 cm³) to 5.16 months for volume >9.1 cm³). Overall 2-year survival was 20.7%. **CONCLUSION:** Results from the first Gamma Knife radiosurgery center in Australia showed that the treatment is feasible and effective, consistent with the international experience. For patients with larger numbers of intracranial metastases, the total volume of the intracranial burden may be of more significance in predicting outcomes. While there appeared to be a difference in survival by histologic origin, this could be related to concurrent systemic immunotherapy available for certain tumors.

[77] Stereotactic Radiosurgery for Multiple Brain Metastases From Renal-Cell Carcinoma.

Clinical genitourinary cancer. 2019;17(2):e273-e280

Wardak Z, Christie A, Bowman A, Stojadinovic S, Nedzi L, Barnett S, Patel T, Mickey B, Whitworth T, Hannan R, Brugarolas J, Timmerman R

PMID: 30595522 DOI: 10.1016/j.clgc.2018.11.006

BACKGROUND: Brain metastases (BM) pose a significant problem in patients with metastatic renal-cell carcinoma (mRCC). Local and systemic therapies including stereotactic radiosurgery (SRS) are rapidly evolving, necessitating reassessments of outcomes for modern patient management. **PATIENTS AND METHODS:** The mRCC patients with BM treated with SRS were reviewed. Patient demographics, clinical history, and SRS treatment parameters were identified. **RESULTS:** Among 268 patients with mRCC treated between 2006 and 2015, 38 patients were identified with BM. A total of 243 BM were treated with SRS with 1 to 26 BMs treated per SRS session (median, 2 BMs). The median (range) BM size was 0.6 (0.2-3.1) cm and median (range) SRS treatment dose was 18 (12-24) Gy. Treated BM local control rates at 1 and 2 years were 91.8% (95% confidence interval, 85.7-95.4) and 86.1% (95% confidence interval, 77.1-91.7), respectively. BM control declined for larger tumors. Survival after 1-year was 57.5% (95% CI 40.2-71.4) for all patients. Survival was not statistically different between patients with < 5 BM versus ≥ 5 BM. Survival was prognostic based on International Metastatic Renal Cell Carcinoma Database (IMDC) risk groups in patients with < 5 BM. Two patients experienced grade 3 radiation necrosis requiring surgical intervention. **CONCLUSION:** SRS is effective in controlling BM in patients with mRCC. Over half of treated patients survive past a year, and no differences in survival were noted in patients with > 5 metastases. Prognostic risk categories based on systemic disease (IMDC) are predictive of survival in this BM population, with limited rates of symptomatic radiation necrosis.

[78] BRAF V600 Mutation and BRAF Kinase Inhibitors in Conjunction With Stereotactic Radiosurgery for Intracranial Melanoma Metastases: A Multicenter Retrospective Study.

Neurosurgery. 2019;84(4):868-880

Mastorakos P, Xu Z, Yu J, Hess J, Qian J, Chatrath A, Taylor DG, Kondziolka D, Warnick R, Chiang V, Sheehan J

PMID: 29846702 DOI: 10.1093/neuros/nyy203

BACKGROUND: The BRAF mutation has been identified as a potent target for the treatment of metastatic melanoma and BRAF inhibitors (BRAFi) have demonstrated promising results against melanoma brain metastases (BM).

OBJECTIVE: To further investigate the effectiveness of this combined treatment regimen. **METHODS:** In this multicenter retrospective cohort study, 198 patients with known BRAF mutation status and treated with stereotactic radiosurgery (SRS) between 2011 and 2015 were identified. Kaplan-Meier methodology and multivariate regression analysis was then used to compare survival based on each parameter. **RESULTS:** The median survival after the diagnosis of BM in patients with BRAF mutation who received BRAFi was increased compared to survival in patients with wild-type BRAF (BRAF wt). In multivariate analysis, the BRAF mutation was an independent, positive prognostic factor with a hazard ratio of 0.59. BRAF mutated Patients who received BRAFi following SRS had improved survival compared to patients who received it before (P < .001) or concurrently (P = .007). PD-1 inhibitors improved survival, with more pronounced effect in patients not carrying the BRAF mutation. Among the patients who were treated with BRAFi, 10.4% developed intracerebral hematoma (ICH), in comparison to 3% of patients who were not treated with BRAFi (P = .03). **CONCLUSION:** In the setting of widespread use of BRAFi, the presence of a BRAF mutation is an independent predictor of better prognosis in patients with melanoma BM that underwent SRS. The effect of BRAFi is optimal when treatment is initiated at least 1 wk following SRS. BRAFi may increase the frequency of asymptomatic ICH.

[79] Efficacy of gamma knife radiosurgery in brain metastases of primary gynecological tumors.

Journal of neuro-oncology. 2019;142(2):283-290

Sadik ZHA, Beerepoot LV, Hanssens PEJ

PMID: 30666465 DOI: 10.1007/s11060-019-03094-2

OBJECTIVE: Gynecological brain metastases (BM) are rare and usually develop as part of widespread disseminated disease. Despite treatment, the majority of these patients do not survive > 1 year due to advanced extracranial disease. The use of Gamma Knife Radiosurgery (GKRS) for gynecological BM is not well known. The goal of this study is to evaluate the efficacy of GKRS for gynecological BM.

METHODS: We performed a retrospective study of patients with gynecological BM who underwent GKRS between 2002 and 2015. A total of 41 patients were included. Outcome measures were local tumor control (LC), development of new BM and/or leptomeningeal disease, overall intracranial progression free survival (PFS) and survival. **RESULTS:** LC was 100%, 92%, 80%, 75% and 67% at 3, 6, 9, 12 and 15 months, respectively. PFS was 90%, 61%, 41%, 23% and 13% at 3, 6, 9, 12 and 15 months, respectively. During follow-up (FU), 18 (44%) patients had intracranial progression. Distant BM occurred in 29% of the patients. Local recurrence and distant recurrence occurred after a mean FU time of 15.5 (2.6-71.9) and 11.4 (2-40) months, respectively. Thirty-one (76%) patients died due to extracranial tumor progression and only 2 (5%) patients died due to progressive intracranial disease. The overall mean survival from time of GKRS was 19 months (1-109). The 6-month, 1-year, and 2-year survival rate from the time of GKRS were 71%, 46%, and 22%, respectively. **CONCLUSION:** GKRS is a good treatment option for controlling gynecological BM. As most patients die due to extracranial tumor progression, their survival might improve with better systemic treatment options in addition to GKRS.

[80] Symptomatic radiation necrosis in brain metastasis patients treated with stereotactic radiosurgery and immunotherapy.

Clinical neurology and neurosurgery. 2019;179:14-18
Weingarten N, Kruser TJ, Bloch O
PMID: 30784894 DOI: 10.1016/j.clineuro.2019.02.010

OBJECTIVES: The association of symptomatic radiation necrosis (RN) with stereotactic radiosurgery (SRS) and immune checkpoint inhibitors (ICIs) in brain metastases patients has been incompletely explored. We aim to discuss the incidence, risk factors, and prognosis of symptomatic RN in patients treated with these modalities. **PATIENTS AND METHODS:** We retrospectively evaluated the incidence of symptomatic RN among all patients with brain metastases treated with both SRS and an ICI at a single academic center. Risk factors for the development of symptomatic RN were determined, along with median overall survival (OS) stratified by the development of RN. **RESULTS:** Between 2010 and 2016, 57 brain metastases patients were treated with both SRS and an ICI. Only 4 (7%) developed symptomatic RN. Symptomatic RN lesions were more likely to be located in the cerebral cortex ($p = 0.019$) and be associated with a primary renal cell carcinoma ($p = 0.032$). Median OS was 32 months for those who developed symptomatic RN and 29 months for all other patients ($p = 0.16$). **CONCLUSION:** Treatment of brain metastases with both SRS and an ICI is an effective modality that poses mild risk for developing symptomatic RN when compared to the risk of RN from SRS alone.

[81] Breast cancer patients with brain metastasis undergoing GKRS.

Breast cancer (Tokyo, Japan). 2019;26(2):147-153
Abu-Khalaf M, Muralikrishnan S, Hatzis C, Canchi D, Yu JB, Chiang V
PMID: 30182250 DOI: 10.1007/s12282-018-0903-3

BACKGROUND: Breast cancer (BC) is the second most common cause of brain metastasis in the United States. Compared to whole brain radiation therapy (WBRT), treatment with gamma-knife radiosurgery (GKRS) offers a better chance at neurocognitive preservation. The goal of our retrospective study is to report the overall survival (OS) in patients receiving GKRS and to identify factors that improve survival outcomes. **METHODS:** The records of 80 patients with primary BC treated with GKRS at the Yale Comprehensive Cancer Center between 2000 and 2013 were reviewed. OS was calculated from the date of first GKRS treatment. Other factors studied were age, Karnofsky performance status (KPS), tumor subtype, having WBRT and/or surgical resection pre- or post-GKRS, and number of brain metastases treated with GKRS. **RESULTS:** Median age was 56.2 years. OS from first GKRS was 13.1 months (95% CI 7.6-21.9). On univariate analysis, improved survival was associated with HER-2 subtype ($p = 0.026$), KPS score > 80 ($p = 0.009$), and good control of systemic disease at time of GKRS ($p = 0.020$). Multivariable analysis detected a significantly longer survival with HER-2 positivity (HR 0.22, 95% CI 0.06-0.76, $p = 0.017$) and a strong trend in patients with craniotomy prior to GKRS (HR 0.13, 95% CI 0.01-1.11, $p = 0.06$). **CONCLUSIONS:** GKRS is a promising therapy for treating brain metastasis from BC, particularly in those with HER-2 positivity and high-performance scores even in those patients with > 5 brain metastases. Furthermore, GKRS may also be a useful adjunct to surgical resection in such patients. High rates of neurological death remain from BC brain metastases; however, and need further investigation.

[82] Clinical efficacy and safety evaluation of pemetrexed combined with radiotherapy in treatment of patients with lung adenocarcinoma brain metastasis.

Oncology letters. 2019;17(3):2874-2880
Zhang G, Zeng R, Wang K, A Y, Li L, Gong X
PMID: 30854063 DOI: 10.3892/ol.2019.9894
Clinical efficacy and adverse reactions of pemetrexed combined with stereotactic gamma-ray radiotherapy in the treatment of patients with lung adenocarcinoma brain metastasis in The First People's Hospital of Yunnan Province were evaluated. A total of 67 patients with lung adenocarcinoma brain metastasis in experimental group were treated with simple pemetrexed chemotherapy, and then with

radiotherapy, followed by pemetrexed chemotherapy. Their treatment results were compared with those of 53 patients treated with simple gamma knife in control group. The results were analyzed by comparing the clinical efficacy, side reactions, serum level changes, and survival between the two groups. Among 67 patients in the experimental group, there were 16 cases of complete response (CR), 39 cases of partial response (PR), 7 cases of stable disease (SD) and 5 cases of progressive disease (PD), with an effective rate of 82.09% (55/67) and a tumor local control rate of 92.54% (62/67). Among 53 patients in the control group, there were 13 cases of CR, 20 cases of PR, 9 cases of SD and 11 cases of PD, with an effective rate of 62.26% (33/53) and a tumor local control rate of 79.25% (42/53). There were statistically significant differences in the effective rate and local control rate between the two groups ($P < 0.05$). The 6-, 12- and 24-month survival rates in experimental group were higher than those in control group ($P < 0.05$). The main adverse reactions after pemetrexed combined with radiotherapy were lower than those after simple radiotherapy ($P < 0.05$). The expression levels of the tumor markers carcinoembryonic antigen (CEA) and cytokeratin fragment antigen 21-1 (CYFRA21-1) in the two groups of patients after treatment were lower than those before treatment ($P < 0.05$). After treatment, the expression levels of serum CEA and CYFRA21-1 in the experimental group were significantly lower than those in the control group ($P < 0.05$). Pemetrexed combined with radiotherapy in the treatment of lung adenocarcinoma brain metastasis is more effective than simple radiotherapy, with lighter adverse reactions, worthy of clinical application and promotion.

[83] Validity of a Recently Proposed Prognostic Grading Index, Brain Metastasis Velocity, for Patients With Brain Metastasis Undergoing Multiple Radiosurgical Procedures.

International journal of radiation oncology, biology, physics. 2019;103(3):631-637
Yamamoto M, Aiyama H, Koiso T, Watanabe S, Kawabe T, Sato Y, Higuchi Y, Kasuya H, Barfod BE
PMID: 30395905 DOI: 10.1016/j.ijrobp.2018.10.036

PURPOSE: This study of our patients with brain metastasis who underwent multiple stereotactic radiosurgery (SRS) procedures aimed to validate whether the recently proposed prognostic grading system, brain metastasis velocity (BMV), is generally applicable. The BMV scores the cumulative number of new brain metastases that developed after the first SRS divided by time (years) since the initial SRS. Patients were categorized into 3 classes by their BMV scores (ie, $< / = 3$, 4-13, and $> / = 14$). **METHODS AND MATERIALS:** This retrospective cohort study was approved by the Tokyo Women's Medical University Institutional Review Board (number 1981). We used our prospectively accumulated database, which included 833 patients who underwent a second SRS procedure for newly detected lesions, using a gamma knife, for brain metastases. Patients who had whole-brain radiation therapy were excluded. The procedures took place during the 19-year period between July 1998 and June 2017. Furthermore, among the 833 patients, 250 underwent a third SRS procedure, and 88 had a fourth SRS procedure. **RESULTS:** The median survival times (MSTs) after the second SRS were 12.9 months (95% confidence interval [CI], 10.2-17.1) for the BMV group with a score of $< / = 3$; 7.5 months (CI, 6.5-9.0) for the group scoring 4 to 13, and 5.1 months (CI, 4.0-5.6) for the group scoring $> / = 14$ ($P = .0001$). The corresponding MSTs after the third SRS were 13.2 months (95% CI, 9.1-21.6), 8.0 months (CI, 6.2-11.2), and 5.7 months (CI, 4.8-7.8; $P = .0001$). Respective MSTs after the fourth SRS were 13.2 months (95% CI, 9.1-21.6), 8.0 months (CI, 6.2-11.2), and 5.7 months (CI, 4.8-7.8; $P < .0001$). The mean BMV score of patients with small cell lung cancer, 24.8, was significantly higher than that of patients with non-small cell lung cancer, 17.7 ($P = .032$). **CONCLUSIONS:** Our present results support the validity of BMV for predicting survival not only after the second SRS but also after the third and fourth SRS.

[84] Outcomes following stereotactic radiosurgery for small to medium-sized brain metastases are exceptionally dependent upon tumor size and prescribed dose.

Neuro-oncology. 2019;21(2):242-251

Moraes FY, Winter J, Atenafu EG, Dasgupta A, Raziee H, Coolens C, Millar BA, Laperriere N, Patel M, Bernstein M, Kongkham P, Zadeh G, Conrad T, Chung C, Berlin A, Shultz DB

PMID: 30265328 DOI: 10.1093/neuonc/noy159

BACKGROUND: At our institution, we have historically treated brain metastasis (BM) ≤ 2 cm in eloquent brain with a radiosurgery (SRS) lower prescription dose (PD) to reduce the risk of radionecrosis (RN). We sought to evaluate the impact of this practice on outcomes. **METHODS:** We analyzed a prospective registry of BM patients treated with SRS between 2008 and 2017. Incidences of local failure (LF) and RN were determined and Cox regression was performed for univariate and multivariate analyses (MVA). **RESULTS:** We evaluated 1533 BM ≤ 2 cm. Median radiographic follow-up post SRS was 12.7 months (1.4-100). Overall, the 2-year incidence of LF was lower for BM treated with PD ≥ 21 Gy (9.3%) compared with PD ≤ 15 Gy (19.5%) (sub-hazard ratio, 2.3; 95% CI: 1.4-3.7; $P = 0.0006$). The 2-year incidence of RN was not significantly higher for the group treated with PD ≥ 21 Gy (9.5%) compared with the PD ≤ 15 Gy group (7.5%) ($P = 0.16$). MVA demonstrated that PD (≤ 15 Gy) and tumor size (> 1 cm) were significantly correlated ($P < 0.05$) with higher rates of LF and RN, respectively. For tumors ≤ 1 cm, when comparing PD ≤ 15 Gy with ≥ 21 Gy, the risks of LF and RN are equivalent. However, for lesions > 1 cm, PD ≥ 21 Gy is associated with a lower incidence of LF without significantly increasing the risk of RN. **CONCLUSION:** Our results indicate that rates of LF or RN following SRS for BM are strongly correlated with size and PD. Based on our results, we now, depending upon the clinical context, consider increasing PD to 21 Gy for BM in eloquent brain, excluding the brainstem.

[85] Stereotactic radiosurgery with concurrent lapatinib is associated with improved local control for HER2-positive breast cancer brain metastases.

Journal of Neurosurgery. 2019;132(2):503-511

Parsai S, Miller JA, Juloori A, Chao ST, Kotecha R, Mohammadi AM, Ahluwalia MS, Murphy ES, Barnett GH, Vogelbaum MA, Angelov L, Peereboom DM, Suh JH
PMID: 30738402 DOI: 10.3171/2018.10.JNS182340

OBJECTIVE: With increasing survival for patients with human epidermal growth factor receptor 2-positive (HER2+) breast cancer in the trastuzumab era, there is an increased risk of brain metastasis. Therefore, there is interest in optimizing intracranial disease control. Lapatinib is a small-molecule dual HER2/epidermal growth factor receptor inhibitor that has demonstrated intracranial activity against HER2+ breast cancer brain metastases. The objective of this study was to investigate the impact of lapatinib combined with stereotactic radiosurgery (SRS) on local control of brain metastases. **METHODS:** Patients with HER2+ breast cancer brain metastases who underwent SRS from 1997-2015 were included. The primary outcome was the cumulative incidence of local failure following SRS. Secondary outcomes included the cumulative incidence of radiation necrosis and overall survival. **RESULTS:** One hundred twenty-six patients with HER2+ breast cancer who underwent SRS to 479 brain metastases (median 5 lesions per patient) were included. Among these, 75 patients had luminal B subtype (hormone receptor-positive, HER2+) and 51 patients had HER2-enriched histology (hormone receptor-negative, HER2+). Forty-seven patients received lapatinib during the course of their disease, of whom 24 received concurrent lapatinib with SRS. The median radiographic follow-up among all patients was 17.1 months. Concurrent lapatinib was associated with reduction in local failure at 12 months (5.7% vs 15.1%, $p < 0.01$). For lesions in the ≤ 75 th percentile by volume, concurrent lapatinib significantly decreased local failure. However, for lesions in the > 75 th percentile (> 1.10 cm³), concurrent lapatinib did not significantly improve local failure. Any use of lapatinib after development of brain metastasis improved median survival compared to SRS without lapatinib (27.3 vs 19.5 months, $p = 0.03$). The 12-month risk of radiation necrosis was consistently lower in the lapatinib

cohort compared to the SRS-alone cohort (1.3% vs 6.3%, $p < 0.01$), despite extended survival. **CONCLUSIONS:** For patients with HER2+ breast cancer brain metastases, the use of lapatinib concurrently with SRS improved local control of brain metastases, without an increased rate of radiation necrosis. Concurrent lapatinib best augments the efficacy of SRS for lesions ≤ 1.10 cm³ in volume. In patients who underwent SRS for HER2+ breast cancer brain metastases, the use of lapatinib at any time point in the therapy course was associated with a survival benefit. The use of lapatinib combined with radiosurgery warrants further prospective evaluation.

[86] Factors influencing the outcome of stereotactic radiosurgery in patients with five or more brain metastases.

Current oncology (Toronto, Ont.). 2019;26(1):e64-e69

Hamel-Perreault E, Mathieu D, Masson-Cote L

PMID: 30853811 DOI: 10.3747/co.25.4244

BACKGROUND: Stereotactic radiosurgery (srs) for patients with 5 or more brain metastases (bmets) is a matter of debate. We report our results with that approach and the factors influencing outcome. **METHODS:** In the 103 patients who underwent srs for the treatment of 5 or more bmets, primary histology was non-small-cell lung cancer (57% of patients). All patients were grouped by Karnofsky performance status and recursive partitioning analysis (rpa) classification. In our cohort, 72% of patients had uncontrolled extracranial disease, and 28% had stable or responding systemic disease. Previous irradiation for 1-4 bmets had been given to 56 patients (54%). The mean number of treated bmets was 7 (range: 5-19), and the median cumulative bmets volume was 2 cm³ (range: 0.06-28 cm³).

RESULTS: Multivariate analyses showed that stable extracranial disease ($p < 0.001$) and rpa ($p = 0.022$) were independent prognostic factors for overall survival (os). Moreover, a cumulative treated bmets volume of less than 6 cm³ (adjusted hazard ratio: 2.54; $p = 0.006$; 95% confidence interval: 1.30 to 4.99) was associated with better os. The total number of bmets had no effect on survival ($p = 0.206$). No variable was found to be predictive of local control. The rpa was significant ($p = 0.027$) in terms of distant recurrence. **CONCLUSIONS:** Our study suggests that srs is a reasonable option for the management of patients with 5 or more bmets, especially with a cumulative treatment volume of less than 6 cm³.

[87] Comparison of Local Control of Brain Metastases With Stereotactic Radiosurgery vs Surgical Resection: A Secondary Analysis of a Randomized Clinical Trial.

JAMA oncology. 2019;5(2):243-247

Churilla TM, Chowdhury IH, Handorf E, Collette L, Collette S, Dong Y, Alexander BM, Kocher M, Soffietti R, Claus EB, Weiss SE

PMID: 30419088 DOI: 10.1001/jamaoncol.2018.4610

Importance: Brain metastases are a common source of morbidity for patients with cancer, and limited data exist to support the local therapeutic choice between surgical resection and stereotactic radiosurgery (SRS). **OBJECTIVE:** To evaluate local control of brain metastases among patients treated with SRS vs surgical resection within the European Organization for the Research and Treatment of Cancer (EORTC) 22952-26001 phase 3 trial. Design, Setting, and Participants: This unplanned, exploratory analysis of the international, multi-institutional randomized clinical trial EORTC 22952-26001 (conducted from 1996-2007) was performed from February 9, 2017, through July 25, 2018. The EORTC 22952-26001 trial randomized patients with 1 to 3 brain metastases to whole-brain radiotherapy vs observation after complete surgical resection or before SRS. Patients in the present analysis were stratified but not randomized according to local modality (SRS or surgical resection) and treated per protocol with 1 to 2 brain metastases and tumors with a diameter of no greater than 4 cm. Interventions: Surgical resection or SRS. Main Outcomes and Measures: The primary end point was local recurrence of treated lesions. Cumulative incidence of local recurrence was calculated according to modality (surgical resection vs SRS) with competing risk regression to adjust for prognostic factors and competing risk of death. **RESULTS:** A total of 268 patients were included in the analysis (66.4% men; median age, 60.7 years [range, 26.9-81.1

years)); 154 (57.5%) underwent SRS and 114 (42.5%) underwent surgical resection. Median follow-up time was 39.9 months (range, 26.0-1982.0 months). Compared with the SRS group, patients undergoing surgical resection had larger metastases (median 28 mm [range, 10-40 mm] vs 20 mm [range, 4-40 mm]; $P < .001$), more frequently had 1 brain metastasis (112 [98.2%] vs 114 [74.0%]; $P < .001$), and differed in location (parietal, 21 [18.4%] vs 61 [39.6%]; posterior fossa, 30 [26.3%] vs 12 [7.8%]; $P < .001$). In adjusted models, local recurrence was similar between the SRS and surgical resection groups (hazard ratio [HR], 1.15; 95% CI, 0.72-1.83). However, when stratified by interval, patients with surgical resection had a much higher risk of early (0-3 months) local recurrence compared with those undergoing SRS (HR, 5.94; 95% CI, 1.72-20.45), but their risk decreased with time (HR for 3-6 months, 1.37 [95% CI, 0.64-2.90]; HR for 6-9 months, 0.75 [95% CI, 0.28-2.00]). At 9 months or longer, the surgical resection group had a lower risk of local recurrence (HR, 0.36; 95% CI, 0.14-0.93). **CONCLUSIONS AND RELEVANCE:** In this exploratory analysis, local control of brain metastases was similar between SRS and surgical resection groups. Stereotactic radiosurgery was associated with improved early local control of treated lesions compared with surgical resection, although the relative benefit decreased with time. Trial Registration: ClinicalTrials.gov Identifier: NCT00002899.

[88] Gamma Knife Radiosurgery for Metastatic Brain Tumors from Cancer of Unknown Primary.

World neurosurgery. 2019;122:e1465-e1471
Matsunaga S, Shuto T, Kobayashi N
PMID: 30468925 DOI: 10.1016/j.wneu.2018.11.086

OBJECTIVE: We retrospectively analyzed treatment efficacy and identified prognostic factors impacting tumor control and survival in patients with brain metastases from cancer of unknown primary (CUP) treated with gamma knife radiosurgery (GKRS). **METHODS:** We retrospectively reviewed the medical records of 87 patients with 520 tumors who underwent GKRS for brain metastases from CUP. **RESULTS:** The median overall survival time after initial GKRS was 6 months. The 6- and 12-month overall survival rates were 79.3% and 14.9%, respectively. Older age ($P = 0.002$), lower Karnofsky Performance Status Index score ($P = 0.026$), extracranial metastases ($P = 0.013$), and multiple brain metastases ($P = 0.007$) were significantly correlated with shorter survival periods. The 6- and 12-month neurologic death rates were 25.3% and 32.2%, respectively. The 6- and 12-month neurologic deterioration rates were 24.1% and 27.6%, respectively. The 6- and 12-month distant brain control failure rates were 21.8% and 24.1%, respectively. The median tumor volume was 1.7 cm³. The median marginal prescription dose was 18 Gy. The 6- and 12-month tumor recurrence rates were 5.1% and 15.7%, respectively. Larger tumor volume ($P < 0.0001$) and lower prescription dose ($P = 0.001$) were significantly correlated with local tumor control failure. Seven patients had symptomatic radiation injury. The 6- and 12-month GKRS-related complication rates were both 6.9%. **CONCLUSIONS:** Our findings suggest that GKRS is a relatively effective and safe treatment for control of tumor progression in patients with brain metastases from CUP. Overall and neurologic survivals were short, but we recommend GKRS treatment to prevent early neurologic dysfunction and death in patients with CUP.

[89] Low-dose Gamma Knife radiosurgery plus whole-brain radiation therapy for patients with 5 or more brain metastases with or without meningeal dissemination.

International journal of clinical oncology. 2019;24(2):161-167
Miyakawa A, Shibamoto Y, Takemoto S, Hirai T, Serizawa T
PMID: 30099697 DOI: 10.1007/s10147-018-1339-7

PURPOSE/OBJECTIVE(S): Radiosurgery plus whole-brain radiotherapy (WBRT) has been reported to be useful for patients with ≤ 4 brain metastases (BM), but we hypothesized that similar treatment may be applicable to patients with > 5 BM with or without meningeal dissemination. The purpose of this study was to evaluate the efficacy and toxicity of low-dose Gamma Knife (GK) followed by WBRT for patients with advanced BM. **MATERIALS/METHODS:**

Major eligibility criteria for this phase II study were: (1) ≥ 5 BM with or without meningeal dissemination and (2) the largest tumor diameter ≤ 4 cm. During 2013-2016, 40 patients (13 men and 27 women) entered the study. Nineteen had meningeal dissemination. The GK dose was 12 Gy at the periphery when the longest diameter was 3-4 cm and 14 Gy when it was < 3 cm. The WBRT dose to the isocenter was 30 Gy in 10 fractions, or 37.5 Gy in 15 fractions for two patients, with an expected survival of > 12 months. The median number of target BM was 17.5. **RESULTS:** After GK plus WBRT for 40 patients, 31 did not develop further intracranial recurrence until death or last follow-up, whereas 9 developed recurrence. With a follow-up period up to 24 months, the overall survival rate was 36% at 12 months and median survival time was 8 months. The cumulative incidence of intracranial recurrence was 25% at 12 months. Toxicity was considered acceptable. **CONCLUSION:** Treatment with low-dose GK followed by WBRT for advanced-stage BM appeared to contribute to local control.

[90] Overall survival and response to radiation and targeted therapies among patients with renal cell carcinoma brain metastases.

Journal of neurosurgery. 2019;:1-9
Juloori A, Miller JA, Parsai S, Kotecha R, Ahluwalia MS, Mohammadi AM, Murphy ES, Suh JH, Barnett GH, Yu JS, Vogelbaum MA, Rini B, Garcia J, Stevens GH, Angelov L, Chao ST
PMID: 30660120 DOI: 10.3171/2018.8.JNS182100

OBJECTIVE: The object of this retrospective study was to investigate the impact of targeted therapies on overall survival (OS), distant intracranial failure, local failure, and radiation necrosis among patients treated with radiation therapy for renal cell carcinoma (RCC) metastases to the brain. **METHODS:** All patients diagnosed with RCC brain metastasis (BM) between 1998 and 2015 at a single institution were included in this study. The primary outcome was OS, and secondary outcomes included local failure, distant intracranial failure, and radiation necrosis. The timing of targeted therapies was recorded. Multivariate Cox proportional-hazards regression was used to model OS, while multivariate competing-risks regression was used to model local failure, distant intracranial failure, and radiation necrosis, with death as a competing risk. **RESULTS:** Three hundred seventy-six patients presented with 912 RCC BMs. Median OS was 9.7 months. Consistent with the previously validated diagnosis-specific graded prognostic assessment (DS-GPA) for RCC BM, Karnofsky Performance Status (KPS) and number of BMs were the only factors prognostic for OS. One hundred forty-seven patients (39%) received vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs). Median OS was significantly greater among patients receiving TKIs (16.8 vs 7.3 months, $p < 0.001$). Following multivariate analysis, KPS, number of metastases, and TKI use remained significantly associated with OS. The crude incidence of local failure was 14.9%, with a 12-month cumulative incidence of 13.4%. TKIs did not significantly decrease the 12-month cumulative incidence of local failure (11.4% vs 14.5%, $p = 0.11$). Following multivariate analysis, age, number of BMs, and lesion size remained associated with local failure. The 12-month cumulative incidence of radiation necrosis was 8.0%. Use of TKIs within 30 days of SRS was associated with a significantly increased 12-month cumulative incidence of radiation necrosis (10.9% vs 6.4%, $p = 0.04$). **CONCLUSIONS:** Use of targeted therapies in patients with RCC BM treated with intracranial SRS was associated with improved OS. However, the use of TKIs within 30 days of SRS increases the rate of radiation necrosis without improving local control or reducing distant intracranial failure. Prospective studies are warranted to determine the optimal timing to reduce the rate of necrosis without detracting from survival.

[91] Radiological Kinetics of Brain Metastases and Clinical Implications for Patients Treated With Stereotactic Radiosurgery.

Clinical oncology (Royal College of Radiologists (Great Britain)). 2019;31(1):34-40
Nicholls LW, Pinkham MB, Bernard A, Lusk R, Watkins T, Hall B, Olson S, Foote MC
PMID: 30279038 DOI: 10.1016/j.clon.2018.09.005
AIMS: Select patients with brain metastases receive stereotactic radiosurgery

(SRS) with the objective of improving survival and intracranial disease control. Brain metastases number and volume are prognostic factors used to inform patient selection. The aim of this study was to assess the rate of change of brain metastases size and number (growth kinetics) between the diagnostic and day of SRS magnetic resonance imaging (MRI) scans. **MATERIALS AND METHODS:** All patients treated with Gamma Knife SRS between October 2015 and April 2017 were included in this single-centre retrospective analysis. Brain metastases number and diameter were recorded at diagnosis and treatment. For patients with multiple brain metastases, the largest lesion was the index lesion. Distant intracranial control and overall survival were reported from the date of SRS. **RESULTS:** In total, 146 patients received 156 episodes of SRS. The median interval between diagnostic and SRS MRI was 20 days (range 1-68). Interval growth in the index lesion of at least 3 mm or the development of a new brain metastasis was noted in 60.2% of patients. This was associated with age less than 60 years ($P = 0.001$), Eastern Cooperative Oncology Group (ECOG) performance status 2 or above ($P = 0.04$), non-small cell lung carcinoma (NSCLC) ($P = 0.03$) or melanoma histologies ($P = 0.05$) and uncontrolled extracranial disease ($P = 0.05$). These patients were also more likely to develop distant intracranial recurrence ($P = 0.046$). Clinically significant growth was not associated with scan interval or differences in overall survival. The Kaplan-Meier estimate of probability of survival at 12 months was 59.3% (95% confidence interval 46.7-75.2%) for all patients. **CONCLUSION:** Intracranial progression between diagnosis and day of SRS is common. Risk factors are uncontrolled extracranial disease, poorer performance status, NSCLC or melanoma histologies and age less than 60 years. These patients would benefit from an MRI closer to treatment to inform patient selection and target delineation for SRS planning.

2018

[92] Quality of life outcomes for brain metastasis patients treated with stereotactic radiosurgery: pre-procedural predictive factors from a prospective national registry.

Journal of neurosurgery. 2018;131(6):1848-1854

Sheehan JP, Grills I, Chiang VL, Dong H, Berg A, Warnick RE, Kondziolka D, Kavanagh B

PMID: 30579284 DOI: 10.3171/2018.8.JNS181599

OBJECTIVE: Stereotactic radiosurgery (SRS) is increasingly used for the treatment of brain metastasis. To date, most studies have focused on survival, radiological response, or surrogate quality endpoints such as Karnofsky Performance Scale status or neurocognitive indices. The current study prospectively evaluated pre-procedural factors impacting quality of life in brain metastasis patients undergoing SRS. **METHODS:** Using a national, cloud-based platform, patients undergoing SRS for brain metastasis were accrued to the registry. Quality of life prior to SRS was assessed using the 5-level EQ-5D (EQ5D-L) validated tool; additionally, patient and treatment attributes were collected. Patient quality of life was assessed as part of routine follow-up after SRS. Factors predicting a difference in the aggregate EQ5D-L score or the subscores were evaluated. Pre-SRS covariates impacting changes in EQ5D-L were statistically evaluated. Statistical analyses were conducted using multivariate linear regression models. **RESULTS:** EQ5D-L results were available for 116 patients. EQ5D-L improvement (average of 0.387) was noted in patients treated with earlier SRS ($p = 0.000175$). Worsening overall EQ5D-L (average of 0.052 per lesion) was associated with an increased number of brain metastases at the time of initial presentation ($p = 0.0399$). Male sex predicted a risk of worsening (average of 0.347) of the pain and discomfort subscore at last follow-up ($p = 0.004205$). Baseline subscores of pain/discomfort were not correlated with pain/discomfort subscores at follow-up ($p = 0.604$), whereas baseline subscores of anxiety/depression were strongly positively correlated with the anxiety/depression follow-up subscores ($p = 0.0039$). **CONCLUSIONS:** After SRS, quality of life was likely to improve in patients treated

early with SRS and worsen in those with a greater number of brain metastases. Sex differences appear to exist regarding pain and discomfort worsening after SRS. Those with high levels of anxiety and depression at SRS may benefit from medical treatment as this particular quality of life factor generally remains unchanged after SRS.

[93] The influence of histology on the response of brain metastases to gamma knife radiosurgery: a propensity score-matched study.

Acta neurochirurgica. 2018;160(12):2379-2386

Kim KH, Lee MH, Cho KR, Choi JW, Kong DS, Seol HJ, Nam DH, Lee JI

PMID: 30413940 DOI: 10.1007/s00701-018-3726-2

BACKGROUND: In terms of response to fractionated radiotherapy, metastatic brain tumors of certain origins are considered radioresistant. **OBJECTIVE:** To determine the influence of "radioresistant" histology on outcomes of brain metastases treated with radiosurgery. **METHODS:** Between 2001 and 2017, 121 patients with brain metastases from renal cell carcinoma (RCC) and 2151 from non-small cell lung cancer (NSCLC) were reviewed. Eighty-seven pairs were derived using propensity score matching. Local progression-free survival (PFS), progression patterns, distant PFS, and overall survival were investigated. **RESULTS:** The median follow-up period was 13.7 months (range, 1.6-78.4 months). A total of 536 lesions were treated using gamma knife radiosurgery (GKS), with a median dose of 20 Gy (range, 12-28 Gy). The actuarial local PFS rates in the RCC group were 91% and 89% at 6 and 12 months, respectively, and did not differ from the NSCLC group (97% and 83% at 6 and 12 months, respectively). Continuous progression, without response to GKS, was noted in seven of the eight progressed RCCs. However, six of the seven progressed NSCLCs showed transient shrinkage before progression. The median distant PFS was 9.3 months (95% CI, 6.3-12.2) in the RCC group and 8.0 months (95% CI, 5.5-10.4) in the NSCLC group. The median overall survival was 16.1 months (95% CI, 11.3-20.8) and 14.9 months (95% CI, 11.9-17.8) in RCC and NSCLC groups, respectively. **CONCLUSION:** Histological differences had no effect on local control in the single high-dose range used for radiosurgery. However, changes in tumor volume during progression varied across tumor histology.

[94] Clinical significance of conformity index and gradient index in patients undergoing stereotactic radiosurgery for a single metastatic tumor.

Journal of neurosurgery. 2018;129(Suppl1):103-110

Aiyama H, Yamamoto M, Kawabe T, Watanabe S, Koiso T, Sato Y, Higuchi Y, Ishikawa E, Yamamoto T, Matsumura A, Kasuya H
PMID: 30544326 DOI: 10.3171/2018.6.GKS181314

OBJECTIVE: Although the conformity index (CI) and the gradient index (GI), which were proposed by Paddick and colleagues, are both logically considered to correlate with good posttreatment results after stereotactic radiosurgery (SRS), this hypothesis has not been confirmed clinically. The authors' aim was to reappraise whether high CI values correlate with reduced tumor progression rates, and whether low GI values correlate with reduced complication incidences. **METHODS:** This was an institutional review board-approved, retrospective cohort study conducted using a prospectively accumulated database including 3271 patients who underwent Gamma Knife SRS for brain metastases (BMs) during the 1998-2016 period. Among the 3271 patients, 925 with a single BM at the time of SRS (335 women and 590 men, mean age 66 [range 24-93] years) were studied. The mean/median CIs were 0.62/0.66 (interquartile range [IQR] 0.53-0.74, range 0.08-0.88) and the mean/median GIs were 3.20/3.09 (IQR 2.83-3.39, range 2.27-11.4). **RESULT:** SSRS-related complications occurred in 38 patients (4.1%), with a median post-SRS interval of 11.5 (IQR 6.0-25.8, maximum 118.0) months. Cumulative incidences of post-SRS complications determined by a competing risk analysis were 2.2%, 3.2%, 3.6%, 3.8%, and 3.9% at the 12th, 24th, 36th, 48th, and 60th post-SRS month, respectively. Multivariable analyses showed that only two clinical factors (i.e., peripheral doses and brain volume receiving ≥ 12 Gy) correlated with complication rates. However, neither CIs nor GIs impacted the incidences of complications. Among the 925 patients, post-

SRS MRI was performed at least once in 716 of them, who were thus eligible for local progression evaluation. Among these 716 patients, local progression was confirmed in 96 (13.4%), with a median post-SRS interval of 10.8 (IQR 6.7-19.5, maximum 59.8) months. Cumulative incidences of local progression determined by a competing risk analysis were 7.7%, 12.6%, 14.2%, 14.8%, and 15.3% at the 12th, 24th, 36th, 48th, and 60th post-SRS month, respectively. Multivariable analyses showed neurological symptoms, extracerebral metastases, repeat SRS, and CIs to correlate with incidences of local progression, whereas GIs had no impact on local tumor progression. Particularly, cumulative incidences of local progression were significantly lower in patients with CIs < 0.65 than in those with CIs \geq 0.65 (adjusted hazard ratio 1.870, 95% confidence interval 1.299-2.843; $p = 0.0034$). **CONCLUSIONS:** To the authors' knowledge, this is the first analysis to focus on the clinical significance of CI and GI based on a large series of patients with BM. Contrary to the majority opinion that dose planning with higher CI and lower GI results in good post-SRS outcomes (i.e., low local progression rates and minimal complications), this study clearly showed that the lower the CIs were, the lower the local progression rates were, and that the GI did not impact complication rates.

[95] Multiinstitutional prospective observational study of stereotactic radiosurgery for patients with multiple brain metastases from non-small cell lung cancer (JLKG0901 study-NSCLC).

Journal of neurosurgery. 2018;129(Suppl1):86-94

Shuto T, Akabane A, Yamamoto M, Serizawa T, Higuchi Y, Sato Y, Kawagishi J, Yamanaka K, Jokura H, Yomo S, Nagano O, Aoyama H
PMID: 30544291 DOI: 10.3171/2018.7.GKS181378

OBJECTIVE: Previous Japanese Leksell Gamma Knife Society studies (JLKG0901) demonstrated the noninferiority of stereotactic radiosurgery (SRS) alone as the initial treatment for patients with 5-10 brain metastases (BMs) compared with those with 2-4 BMs in terms of overall survival and most secondary endpoints. The authors studied the aforementioned treatment outcomes in a subset of patients with BMs from non-small cell lung cancer (NSCLC). **METHODS:** Patients with initially diagnosed BMs treated with SRS alone were enrolled in this prospective observational study. Major inclusion criteria were the existence of up to 10 tumors with a maximum diameter of less than 3 cm each, a cumulative tumor volume of less than 15 cm³, and no leptomeningeal dissemination in patients with a Karnofsky Performance Scale score of 70% or better. **RESULTS:** Among 1194 eligible patients, 784 with NSCLC were categorized into 3 groups: group A (1 tumor, $n = 299$), group B (2-4 tumors, $n = 342$), and group C (5-10 tumors, $n = 143$). The median survival times were 13.9 months in group A, 12.3 months in group B, and 12.8 months in group C. The survival curves of groups B and C were very similar (hazard ratio [HR] 1.037; 95% CI 0.842-1.277; $p < 0.0001$, noninferiority test). The crude and cumulative incidence rates of neurological death, deterioration of neurological function, newly appearing lesions, and leptomeningeal dissemination did not differ significantly between groups B and C. SRS-induced complications occurred in 145 (12.1%) patients during the median post-SRS period of 9.3 months (IQR 4.1-17.4 months), including 46, 54, 29, 11, and 5 patients with a Common Terminology Criteria for Adverse Events v3.0 grade 1, 2, 3, 4, or 5 complication, respectively. The cumulative incidence rates of adverse effects in groups A, B, and C 60 months after SRS were 13.5%, 10.0%, and 12.6%, respectively (group B vs C: HR 1.344; 95% CI 0.768-2.352; $p = 0.299$). The 60-month post-SRS rates of neurocognitive function preservation were 85.7% or higher, and no significant differences among the 3 groups were found. **CONCLUSIONS:** In this subset analysis of patients with NSCLC, the noninferiority of SRS alone for the treatment of 5-10 versus 2-4 BMs was confirmed again in terms of overall survival and secondary endpoints. In particular, the incidence of neither post-SRS complications nor neurocognitive function preservation differed significantly between groups B and C. These findings further strengthen the already-reported noninferiority hypothesis of SRS alone for the treatment of patients with 5-10 BMs.

[96] Clinical outcomes of intracranial solitary fibrous tumor and hemangiopericytoma: analysis according to the 2016 WHO classification of central nervous system tumors.

Journal of neurosurgery. 2018;129(6):1384-1396

Kim BS, Kim Y, Kong DS, Nam DH, Lee JI, Suh YL, Seol HJ
PMID: 29372881 DOI: 10.3171/2017.7.JNS171226

OBJECTIVE: The authors conducted this retrospective study to investigate the clinical outcomes of intracranial solitary fibrous tumor (SFT) and hemangiopericytoma (HPC), defined according to the 2016 WHO classification of central nervous system (CNS) tumors. **METHODS:** Histopathologically proven intracranial SFT and HPC cases treated in the period from June 1996 to September 2014 were retrospectively reviewed and analyzed. Two neuropathologists reviewed pathological slides and regraded the specimens according to the 2016 WHO classification. Factors associated with progression-free survival (PFS) and overall survival (OS) were statistically evaluated with uni- and multivariate analyses. **RESULTS:** The records of 47 patients-10 with SFT, 33 with HPC, and 4 with anaplastic HPC-were reviewed. A malignant transition from conventional SFT to WHO grade III SFT/HPC was observed in 2 cases, and 13 HPC cases were assigned grade III SFT/HPC. Mean and median follow-ups were 114.6 and 94.7 months, respectively (range 7.1-366.7 months). Gross-total resection (GTR) was significantly associated with longer PFS and OS ($p = 0.012$ for both), and adjuvant radiation therapy versus no such therapy led to significantly longer PFS ($p = 0.018$). Extracranial metastases to the liver, bone, lung, spine, and kidney occurred in 10 patients (21.3%). Grade III SFT/HPC was strongly correlated with the development of extracranial metastases ($p = 0.031$). **CONCLUSIONS:** The 2016 WHO classification of CNS tumors reflected the different types of pathological malignant progression and clinical outcomes better than prior classifications. Gross-total resection should be the primary treatment goal in patients with SFT/HPC, regardless of the pathological grade, and radiation can be administered as adjuvant therapy for patients with SFT/HPC that shows an aggressive phenotype or that is not treated with GTR.

[97] Assessment of motion error for frame-based and noninvasive mask-based fixation using the Leksell Gamma Knife Icon radiosurgery system.

Journal of neurosurgery. 2018;129(Suppl1):133-139

Carminucci A, Nie K, Weiner J, Hargreaves E, Danish SF
PMID: 30544303 DOI: 10.3171/2018.7.GKS181516

OBJECTIVE: The Leksell Gamma Knife Icon (GK Icon) radiosurgery system can utilize cone-beam computed tomography (CBCT) to evaluate motion error. This study compares the accuracy of frame-based and frameless mask-based fixation using the Icon system. **METHODS:** A retrospective cohort study was conducted to evaluate patients who had undergone radiosurgery with the GK Icon system between June and December 2017. Patients were immobilized in either a stereotactic head frame or a noninvasive thermoplastic mask with stereotactic infrared (IR) camera monitoring. Setup error was defined as displacement of the skull in the stereotactic space upon setup as noted on pretreatment CBCT compared to its position in the stereotactic space defined by planning MRI for frame patients and defined as skull displacement on planning CBCT compared to its position on pretreatment CBCT for mask patients. For frame patients, the intrafractionation motion was measured by comparing pretreatment and posttreatment CBCT. For mask patients, the intrafractionation motion was evaluated by comparing pretreatment CBCT and additional CBCT obtained during the treatment. The translational and rotational errors were recorded. **RESULTS:** Data were collected from 77 patients undergoing SRS with the GK Icon. Sixty-four patients underwent frame fixation, with pre- and posttreatment CBCT studies obtained. Thirteen patients were treated using mask fixation to deliver a total of 33 treatment fractions. Mean setup and intrafraction translational and rotation errors were small for both fixation systems, within 1 mm and 1 degrees in all axes. Yet mask fixation demonstrated significantly larger intrafraction errors than frame fixation. Also, there was greater variability in both setup and intrafraction errors for mask fixation than for frame fixation in all translational

and rotational directions. Whether the GK treatment was for metastasis or nonmetastasis did not influence motion uncertainties between the two fixation types. Additionally, monitoring IR-based intrafraction motion for mask fixation—i.e., the number of treatment stoppages due to reaching the IR displacement threshold—correlated with increasing treatment time. **CONCLUSIONS:** Compared to frame-based fixation, mask-based fixation demonstrated larger motion variations. The variability in motion error associated with mask fixation must be taken into account when planning for small lesions or lesions near critical structures.

[98] Three-stage Gamma Knife treatment for metastatic brain tumors larger than 10 cm³: a 2-institute study including re-analyses of earlier results using competing risk analysis.

Journal of neurosurgery. 2018;129(Suppl1):77-85

Yamamoto M, Higuchi Y, Serizawa T, Kawabe T, Nagano O, Sato Y, Koiso T, Watanabe S, Aiyama H, Kasuya H
PMID: 30544297 DOI: 10.3171/2018.7.GKS181392

OBJECTIVE: The results of 3-stage Gamma Knife treatment (3-st-GK-Tx) for relatively large brain metastases have previously been reported for a series of patients in Chiba, Japan (referred to in this study as the C-series). In the current study, the authors reappraised, using a competing risk analysis, the efficacy and safety of 3-st-GK-Tx by comparing their experience with that of the C-series.

METHODS: This was a retrospective cohort study. Among 1767 patients undergoing GK radiosurgery for brain metastases at Mito Gamma House during the 2005-2015 period, 78 (34 female, 44 male; mean age 65 years, range 35-86 years) whose largest tumor was > 10 cm³, treated with 3-st-GK-Tx, were studied (referred to in this study as the M-series). The target volumes were covered with a 50% isodose gradient and irradiated with a peripheral dose of 10 Gy at each procedure. The interval between procedures was 2 weeks. Because competing risk analysis had not been employed in the published C-series, the authors reanalyzed the previously published data using this method. **RESULTS:** The overall median survival time after 3-st-GK-Tx was 8.3 months (95% CI 5.6-12.0 months) in the M-series and 8.6 months (95% CI 5.5-10.6 months) in the C-series ($p = 0.41$). Actuarial survival rates at the 6th and 12th post-3-st-GK-Tx months were, respectively, 55.1% and 35.2% in the M-series and 62.5% and 26.4% in the C-series (HR 1.175, 95% CI 0.790-1.728, $p = 0.42$). Cumulative incidences at the 12th post-3-st-GK-Tx, determined by competing risk analyses, of neurological deterioration (14.2% in C-series vs 12.8% in M-series), neurological death (7.2% vs 7.7%), local recurrence (4.8% vs 6.2%), repeat SRS (25.9% vs 18.0%), and SRS-related complications (2.3% vs 5.1%) did not differ significantly between the 2 series. **CONCLUSIONS:** There were no significant differences in post-3-st-GK-Tx results between the 2 series in terms of overall survival times, neurological death, maintained neurological status, local control, repeat SRS, and SRS-related complications. The previously published results (C-series) are considered to be validated by the M-series results.

[99] Prognostic grading system specifically for elderly patients with brain metastases after stereotactic radiosurgery: a 2-institution study.

Journal of neurosurgery. 2018;129(Suppl1):95-102

Yamamoto M, Serizawa T, Higuchi Y, Nagano O, Aiyama H, Koiso T, Watanabe S, Kawabe T, Sato Y, Kasuya H
PMID: 30544299 DOI: 10.3171/2018.7.GKS181458

OBJECTIVE: With the aging of the population, increasing numbers of elderly patients with brain metastasis (BM) are undergoing stereotactic radiosurgery (SRS). Among recently reported prognostic grading indexes, only the basic score for brain metastases (BSBM) is applicable to patients 65 years or older. However, the major weakness of this system is that no BM-related factors are graded. This prompted the authors to develop a new grading system, the elderly-specific (ES)-BSBM. **METHODS:** For this IRB-approved, retrospective cohort study, the authors used their prospectively accumulated database comprising 3267 consecutive patients undergoing Gamma Knife SRS for BMs during the 1998-2016

period at the Mito GammaHouse. Among these 3267 patients, 1789 patients ≥ 65 years of age were studied (Yamamoto series [Y-series]). Another series of 1785 patients ≥ 65 years of age in whom Serizawa and colleagues performed Gamma Knife SRS during the same period (Serizawa series [S-series]) was used for validity testing of the ES-BSBM. **RESULTS:** Two factors were identified as strongly impacting longer survival after SRS by means of multivariable analysis using the Cox proportional hazard model with a stepwise selection procedure. These factors are the number of tumors (solitary vs multiple: HR 1.450, 95% CI 1.299-1.621; $p < 0.0001$) and cumulative tumor volume (≤ 15 cm³ vs > 15 cm³: HR 1.311, 95% CI 1.078-1.593; $p = 0.0067$). The new index is the addition of scores 0 and 1 for these 2 factors to the BSBM. The ES-BSBM system is based on categorization into 3 classes by adding these 2 scores to those of the original BSBM. Each ES-BSBM category has 2 possible scores. For the category ES-BSBM 4-5, the score is either 4 or 5; for ES-BSBM 2-3, the score is either 2 or 3; and for ES-BSBM 0-1, the score is either 0 or 1. In the Y-series, the median survival times (MSTs, months) after SRS were 17.5 (95% CI 15.4-19.3) in ES-BSBM 4-5, 6.9 (95% CI 6.4-7.4) in ES-BSBM 2-3, and 2.8 (95% CI 2.5-3.6) in ES-BSBM 0-1 ($p < 0.0001$). Also, in the S-series, MSTs were, respectively, 20.4 (95% CI 17.2-23.4), 7.9 (95% CI 7.4-8.5), and 3.2 (95% CI 2.8-3.6) ($p < 0.0001$). The ES-BSBM system was shown to be applicable to patients with all primary tumor types as well as to those 80 years or older. **CONCLUSIONS:** The authors found that the addition of the number of tumors and cumulative tumor volume as scoring factors to the BSBM system significantly improved the prognostic value of this index. The present study is strengthened by testing the ES-BSBM in a different patient group.

[100] Surgical resection and postoperative radiosurgery versus staged radiosurgery for large brain metastases.

Journal of neuro-oncology. 2018;140(3):749-756

Dohm AE, Hughes R, Wheless W, Lecompte M, Lanier C, Ruiz J, Watabe K, Xing F, Su J, Cramer C, Laxton A, Tatter S, Chan MD
PMID: 30367382 DOI: 10.1007/s11060-018-03008-8

PURPOSE: The purpose of this study was to retrospectively evaluate the new treatment paradigm of staged stereotactic radiosurgery (SRS) for the treatment of large brain metastases (BM) compared to the standard of surgical resection followed by SRS. **METHODS:** We evaluated 78 patients with large BM treated 2012-2017 with surgical resection and postoperative SRS (surgery + SRS) or staged SRS separated by 1 month. Overall survival (OS) was estimated using the Kaplan Meier method and compared across groups using the log-rank test. Cumulative incidence of neurologic death and local and distant brain failure (LF, DBF) were estimated using competing risk methodology. **RESULTS:** Forty patients were treated with surgery + SRS and 38 patients were treated with staged SRS. Median follow-up was 23.2 months (95% CI 20.5-39.3). Median OS was 13.2 months for staged SRS compared to surgery + SRS 9.7 months ($p = 0.53$). Cumulative incidence of neurologic death at 1 year was 23% after surgery + SRS, 27% after staged SRS ($p = 0.69$); cumulative incidence of LF at 1 year was 6% and 8% ($p = 0.65$) and 1-year DBF was 59% and 21% ($p < 0.01$). Overall rates of leptomeningeal failure and radiation necrosis were similar between the groups ($p = 0.63$ and $p = 1.0$). **CONCLUSIONS:** Though surgery and postoperative SRS is the standard, staged SRS represents an attractive treatment paradigm for treating large BM without sacrificing LC or survival, and potentially decreases DBF. Prospective studies are needed to validate these findings.

[101] Estimating survival for renal cell carcinoma patients with brain metastases: an update of the Renal Graded Prognostic Assessment tool.

Neuro-oncology. 2018;20(12):1652-1660

Sperduto PW, Deegan BJ, Li J, Jethwa KR, Brown PD, Lockney N, Beal K, Rana NG, Attia A, Tseng CL, Sahgal A, Shanley R, Sperduto WA, Lou E, Zahra A, Buatti JM, Yu JB, Chiang V, Molitoris JK, Masucci L, Roberge D, Shi DD, Shih HA, Olson A, Kirkpatrick JP, Braunstein S, Sneed P, Mehta MP
PMID: 30418657 DOI: 10.1093/neuonc/noy099

BACKGROUND: Brain metastases are a common complication of renal cell

carcinoma (RCC). Our group previously published the Renal Graded Prognostic Assessment (GPA) tool. In our prior RCC study (n = 286, 1985-2005), we found marked heterogeneity and variation in outcomes. In our recent update in a larger, more contemporary cohort, we identified additional significant prognostic factors. The purpose of this study is to update the original Renal-GPA based on the newly identified prognostic factors. **METHODS:** A multi-institutional retrospective institutional review board-approved database of 711 RCC patients with new brain metastases diagnosed from January 1, 2006 to December 31, 2015 was created. Clinical parameters and treatment were correlated with survival. A revised Renal GPA index was designed by weighting the most significant factors in proportion to their hazard ratios and assigning scores such that the patients with the best and worst prognoses would have a GPA of 4.0 and 0.0, respectively. **RESULTS:** The 4 most significant factors were Karnofsky performance status, number of brain metastases, extracranial metastases, and hemoglobin. The overall median survival was 12 months. Median survival for GPA groups 0-1.0, 1.5-2.0, 2.5-3, and 3.5-4.0 (n = 25, 27, 30 and 17) was 4, 12, 17, and 35 months, respectively. **CONCLUSION:** The updated Renal GPA is a user-friendly tool that will help clinicians and patients better understand prognosis, individualize clinical decision making and treatment selection, provide a means to compare retrospective literature, and provide more robust stratification of future clinical trials in this heterogeneous population. To simplify use of this tool in daily practice, a free online application is available at brainmetgpa.com.

[102] Complications after stereotactic radiosurgery for brain metastases: Incidences, correlating factors, treatments and outcomes.

Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2018;129(2):364-369

Aiyama H, Yamamoto M, Kawabe T, Watanabe S, Koiso T, Sato Y, Higuchi Y, Ishikawa E, Yamamoto T, Matsumura A, Kasuya H, Barford BE
PMID: 30293644 DOI: 10.1016/j.radonc.2018.08.018

BACKGROUND AND PURPOSE: Complications after stereotactic radiosurgery (SRS) for brain metastases (BMs) were analyzed in detail using our database including nearly 3000 BM patients. **MATERIALS AND METHODS:** This was an institutional review board-approved, retrospective cohort study using our prospectively accumulated database including 3271 consecutive patients who underwent gamma knife SRS for BMs during the 1998-2016 period. Excluding four patients lost to follow-up, 112 with three-staged treatment and 189 with post-operative irradiation, 2966 who underwent a single-session of SRS only as radical irradiation were studied. **RESULTS:** The overall median survival time after SRS was 7.8 (95% CI; 7.4-8.1) months. Post-SRS complications occurred in 86 patients (2.9%) 1.9-211.4 (median; 24.0, IQR; 12.0-64.6) months after treatment. RTOG neurotoxicity grades were 2, 3 and 4 in 58, 25 and 3 patients, respectively. Cumulative incidences determined with a competing risk analysis were 1.4%, 2.2%, 2.4%, 2.6% and 2.9% at the 12th, 24th, 36th, 48th and 60th post-SRS month, respectively. Among various pre-SRS clinical factors and radiosurgical parameters, multivariable analyses demonstrated solitary tumor (Adjusted HR; 0.584, 95% CI; 0.381-0.894, p=0.0133), controlled primary cancer (Adjusted HR; 2.595, 95% CI; 1.646-4.091, p<0.0001), no extra-cerebral metastases (Adjusted HR; 1.608, 95% CI; 1.028-2.514, p=0.0374), KPS \geq 80% (Adjusted HR; 2.715, 95% CI; 1.245-5.924, p=0.0121) and largest tumor volume \geq 3.3cc (Adjusted HR; 0.516, 95% CI; 0.318-0.836, p=0.0072) to be independently significant predictors of a higher incidence of complications. **CONCLUSION:** The post-SRS complication incidence is acceptably low (2.9%). Meticulous long-term follow-up after SRS is crucial for all patients.

[103] Evolution in the role of stereotactic radiosurgery in patients with multiple brain metastases: An international survey.

Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2018;57:6-12

Dutta SW, Sheehan JP, Niranjan A, Lunsford LD, Trifiletti DM
PMID: 30145088 DOI: 10.1016/j.jocn.2018.08.029

OBJECTIVE: Currently no firm consensus exists regarding utilization of stereotactic radiosurgery (SRS) alone versus whole brain radiation (WBRT)+/- SRS in patients with multiple brain metastases. The International Gamma Knife Research Foundation conducted a survey to review international practice patterns. **METHODS:** Through 2 international radiosurgery societies, clinicians who are involved in the radiosurgical management of patients with brain metastases were invited to complete a questionnaire. Respondents selected therapeutic options based on brief case vignettes and could select (1) SRS alone, (2) SRS with adjuvant WBRT, (3) WBRT alone, or (4) omission of upfront local radiation. **RESULTS:** A total of 71 respondents replied to the survey, including 41 radiation oncologists (57%), 24 neurosurgeons (34%), and 6 (8%) other clinicians. For a patient with 7 brain metastases (NSCLC), all under 1cm, and stable extracranial disease, 77% would perform SRS alone and 17% would recommend WBRT alone. For a patient with 7 or more brain metastases, the majority selected SRS alone, irrespective of tumor histology (p>0.5). However, neurosurgeons would more often utilize SRS alone or SRS combined with WBRT compared to radiation oncologists (p=0.002). Key clinical factors in selection were KPS (82% of respondents), total tumor volume (81%), number (80%), and less-so histology (42%). **CONCLUSION:** Regardless of number of metastases, patients with small total volume of brain disease, high KPS, or who are receiving novel therapies are often recommended to undergo SRS. Neurosurgeons more often recommend SRS, emphasizing the importance of additional studies to clarify the role of SRS in these patients.

[104] Tailored Treatment Options for Patients with Brain Metastases by a Relocatable Frame System with Gamma Knife Radiosurgery.

World neurosurgery. 2018;119:e338-e348

Ye K, Samuthrat T, Hu C, Tong Y

PMID: 30059780 DOI: 10.1016/j.wneu.2018.07.157

OBJECTIVE: To report on our experience with the Elekta Extend system, a relocatable frame system used in patients with brain metastases for single-session, hypofractionated, or staged hypofractionated Gamma Knife radiosurgery (GKRS); and the evaluation of its efficacy. **METHODS:** From March 2014 to September 2016, 856 patients with brain metastases underwent GKRS at our hospital. Of them, 35 patients who were retrospectively investigated, were selected for treatment with GKRS using the relocatable frame system. Individualized treatment strategy was chosen according to prior treatment history, number, size and location of tumor, or tumor harboring gene mutation. **RESULTS:** Thirty-two (91.4%) patients underwent treatment with hypofractionated GKRS or staged hypofractionated GKRS, whereas 3 (8.6%) patients underwent single session GKRS. The mean radial setup difference from the reference measurements was 0.50 +/- 0.16 mm. The median follow-up time after GKRS with the Extend system was 12 months (range, 1-45 months). The median overall survival time was 12 months (95% confidence interval 6.43-17.57). On multivariable analysis, performance status and extracranial metastases were independently prognostic factors for overall survival. Radiation necrosis developed in 4 cases (11.4%) during the follow-up period (2 with common terminology criteria for adverse events grade 2 and 2 with its grade 3). **CONCLUSIONS:** The relocatable frame system can maintain submillimetric accuracy and provide tailored treatment option with reasonable tumor control and good survival benefits in selected patients with brain metastases. Especially, hypofractionated GKRS or staged hypofractionated GKRS with noninvasive frame is a safe and effective treatment option for large brain metastases or tumor adjacent to eloquent structures.

[105] Immune checkpoint inhibitors and radiosurgery for newly diagnosed melanoma brain metastases.

Journal of neuro-oncology. 2018;140(1):55-62

Robin TP, Breeze RE, Smith DE, Rusthoven CG, Lewis KD, Gonzalez R, Brill A, Saiki R, Stuhr K, Gaspar LE, Karam SD, Raben D, Kavanagh BD, Nath SK, Liu AK
PMID: 29909499 DOI: 10.1007/s11060-018-2930-5

INTRODUCTION: Brain metastases are common in metastatic melanoma and radiosurgery is often utilized for local control. Immune checkpoint inhibitors

(CPIs) play a central role in contemporary melanoma management; however, there is limited data exploring outcomes and potential toxicities for patients treated with CPIs and radiosurgery. **METHODS:** We retrospectively identified all consecutive cases of newly diagnosed melanoma brain metastases (MBM) treated with Gamma Knife radiosurgery at a single institution between 2012 and 2017, and included only patients that initiated CPIs within 8 weeks before or after radiosurgery. **RESULTS:** Thirty-eight patients were included with a median follow-up of 31.6 months. Two-year local control was 92%. Median time to out-of-field CNS and extra-CNS progression were 8.4 and 7.9 months, respectively. Median progression-free survival (PFS) was 3.4 months and median overall survival (OS) was not reached (NR). Twenty-five patients (66%) received anti-CTLA4 and 13 patients (34%) received anti-PD-1+/-anti-CTLA4. Compared with anti-CTLA4, patients that received anti-PD-1+/-anti-CTLA4 had significant improvements in time to out-of-field CNS progression ($p = 0.049$), extra-CNS progression ($p = 0.015$), and PFS ($p = 0.043$), with median time to out-of-field CNS progression of NR vs. 3.1 months, median time to extra-CNS progression of NR vs. 4.4 months, and median PFS of 20.3 vs. 2.4 months. Six patients (16%) developed grade ≥ 2 CNS toxicities (grade 2: 3, grade 3: 3, grade 4/5: 0). **CONCLUSIONS:** Excellent outcomes were observed in patients that initiated CPIs within 8 weeks of undergoing radiosurgery for newly diagnosed MBM. There appears to be an advantage to anti-PD-1 or combination therapy compared to anti-CTLA4.

[106] Stereotactic radiosurgery for brain metastases from malignant melanoma and the impact of hemorrhagic metastases.

Journal of neuro-oncology. 2018;140(1):83-88

Bauer-Nilsen K, Trifiletti DM, Chatrath A, Ruiz-Garcia H, Marchan E, Peterson J, May BC, Sheehan JP

PMID: 29926319 DOI: 10.1007/s11060-018-2933-2

INTRODUCTION: Stereotactic radiosurgery (SRS) is a common treatment modality among patients with brain metastases, particularly from malignant melanoma. Our objective was to investigate the difference in local control, toxicity, and survival among patients with hemorrhagic and solid melanoma brain metastases. **METHODS:** We collected demographic, treatment, local control, toxicity, and survival for 134 patients with a total of 936 intracranial melanoma metastases who underwent SRS between 1998 and 2015. Pre-radiosurgical diagnostic imaging was reviewed for evidence of hemorrhage (melanin-containing or clearly hemorrhagic). **RESULTS:** The cohort consisted of 92 men and 42 women with a mean age of 61.7 years (range 21.2-84.9) at the time of radiosurgery. Overall survival of patients with brain metastases from malignant melanoma was 42, 31, 12% at 12, 24, and 72 months from date of first SRS. At 6 months, 43% of the patients with hemorrhagic metastases had local tumor control compared to 83% of solid melanoma metastases ($p < 0.001$). No significant difference in toxicity was noted between the two groups. Factors that were significantly associated with time to local tumor progression on multivariate analysis include prior WBRT (HR 1.62, $p = 0.003$), prior chemotherapy (HR 0.69, $p = 0.011$), margin dose (HR 0.88, $p < 0.001$) and radiographic features of melanin deposition (HR 3.73, $p < 0.001$), or clear hemorrhage (HR 2.20, $p < 0.001$). **CONCLUSIONS:** Our findings demonstrate that hemorrhagic intracranial melanoma metastases are associated with inferior local tumor control when treated with SRS, as compared to solid tumors. These results highlight the importance of early radiosurgery among patients with melanoma brain metastases before hemorrhage occurs.

[107] Efficacy of brain radiotherapy plus EGFR-TKI for EGFR-mutated non-small cell lung cancer patients who develop brain metastasis.

Archives of medical science : AMS. 2018;14(6):1298-1307

Wang W, Song Z, Zhang Y

PMID: 30393484 DOI: 10.5114/aoms.2018.78939

INTRODUCTION: To analyze the appropriate treatment methods or timing to use epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and brain radiation treatment (RT) for symptomatic and asymptomatic brain metastases (BM) in patients with EGFR mutation non-small cell lung cancer (NSCLC). **MATERIAL**

AND METHODS: We retrospectively studied patients diagnosed with EGFR gene mutated NSCLC who developed brain metastasis between June 2006 and December 2015 at Zhejiang Cancer Hospital. Treatment data were assessed in 181 patients with 49 symptomatic BM and 132 asymptomatic BM retrospectively.

RESULTS: In 49 symptomatic BM patients, the median OS of the stereotactic radiosurgery (SRS)-treated group was longer than in the whole brain radiotherapy (WBRT) group (37.7 vs. 21.1 months) ($p = 0.194$). In the group of 132 asymptomatic brain metastasis patients, the median overall survival (mOS) was longer in upfront brain radiotherapy compared with the upfront TKI group (24.9 vs. 17.4 months) ($p = 0.035$). In further analysis regarding the timing of using radiotherapy, out of all 74 patients, 33 underwent concurrent TKI and brain radiation, 13 received TKI after first-line RT treatment and 28 patients received radiotherapy after TKI failure. The intracranial progression free survival (iPFS) of the three groups was 11.1 months, 11.3 months and 8.1 months ($p = 0.032$), respectively. The mOS of the three groups was 21.9 months, 26.2 months and 17.1 months, respectively ($p = 0.085$). **CONCLUSIONS:** Our research indicated that delayed brain RT may result in inferior iPFS in EGFR mutated NSCLC patients with asymptomatic brain metastases, but no OS benefit was obtained. In addition, our study revealed that patients treated with SRS had a significantly longer OS for symptomatic BM. Future prospective study of the optimal management strategy with WBRT or SRS and TKI for this patient cohort is urgently needed.

[108] Comparison of treatment results between 3- and 2-stage Gamma Knife radiosurgery for large brain metastases: a retrospective multi-institutional study.

Journal of neurosurgery. 2018;131(1):227-237

Serizawa T, Higuchi Y, Yamamoto M, Matsunaga S, Nagano O, Sato Y, Aoyagi K, Yomo S, Koiso T, Hasegawa T, Nakazaki K, Moriki A, Kondoh T, Nagatomo Y, Okamoto H, Kohda Y, Kawai H, Shidoh S, Shibasaki T, Onoue S, Kenai H, Inoue A, Mori H

PMID: 30192195 DOI: 10.3171/2018.4.JNS172596

OBJECTIVE: In order to obtain better local tumor control for large (i.e., > 3 cm in diameter or > 10 cm³ in volume) brain metastases (BMs), 3-stage and 2-stage Gamma Knife surgery (GKS) procedures, rather than a palliative dose of stereotactic radiosurgery, have been proposed. Here, authors conducted a retrospective multi-institutional study to compare treatment results between 3-stage and 2-stage GKS for large BMs. **METHODS:** This retrospective multi-institutional study involved 335 patients from 19 Gamma Knife facilities in Japan. Major inclusion criteria were 1) newly diagnosed BMs, 2) largest tumor volume of 10.0-33.5 cm³, 3) cumulative intracranial tumor volume ≤ 50 cm³, 4) no leptomeningeal dissemination, 5) no more than 10 tumors, and 6) Karnofsky Performance Status 70% or better. Prescription doses were restricted to between 9.0 and 11.0 Gy in 3-stage GKS and between 11.8 and 14.2 Gy in 2-stage GKS. The total treatment interval had to be within 6 weeks, with at least 12 days between procedures. There were 114 cases in the 3-stage group and 221 in the 2-stage group. Because of the disproportion in patient numbers and the pre-GKS clinical factors between these two GKS groups, a case-matched study was performed using the propensity score matching method. Ultimately, 212 patients (106 from each group) were selected for the case-matched study. Overall survival, tumor progression, neurological death, and radiation-related adverse events were analyzed. **RESULTS:** In the case-matched cohort, post-GKS median survival time tended to be longer in the 3-stage group (15.9 months) than in the 2-stage group (11.7 months), but the difference was not statistically significant ($p = 0.65$). The cumulative incidences of tumor progression (21.6% vs 16.7% at 1 year, $p = 0.31$), neurological death (5.1% vs 6.0% at 1 year, $p = 0.58$), or serious radiation-related adverse events (3.0% vs 4.0% at 1 year, $p = 0.49$) did not differ significantly. **CONCLUSIONS:** This retrospective multi-institutional study showed no differences between 3-stage and 2-stage GKS in terms of overall survival, tumor progression, neurological death, and radiation-related adverse events. Both 3-stage and 2-stage GKS performed according to the aforementioned protocols are good treatment options in selected patients with large BMs.

[109] Repeat Stereotactic Radiosurgery for Recurred Metastatic Brain Tumors.

Journal of Korean Neurosurgical Society. 2018;61(5):633-639

Kim IY, Jung S, Jung TY, Moon KS, Jang WY, Park JY, Song TW, Lim SH
PMID: 30064202 DOI: 10.3340/jkns.2017.0238

OBJECTIVE: We investigated the outcomes of repeat stereotactic radiosurgery (SRS) for metastatic brain tumors that locally recurred despite previous SRS, focusing on the tumor control. **METHODS:** A total of 114 patients with 176 locally recurring metastatic brain tumors underwent repeat SRS after previous SRS. The mean age was 59.4 years (range, 33 to 85), and there were 68 male and 46 female patients. The primary cancer types were non-small cell lung cancer (n=67), small cell lung cancer (n=12), gastrointestinal tract cancer (n=15), breast cancer (n=10), and others (n=10). The number of patients with a single recurring metastasis was 95 (79.8%), and another 19 had multiple recurrences. At the time of the repeat SRS, the mean volume of the locally recurring tumors was 5.94 mL (range, 0.42 to 29.94). We prescribed a mean margin dose of 17.04 Gy (range, 12 to 24) to the isodose line at the tumor border primarily using a 50% isodose line. **RESULTS:** After the repeat SRS, we obtained clinical and magnetic resonance imaging follow-up data for 84 patients (73.7%) with a total of 108 tumors. The tumor control rate was 53.5% (58 of the 108), and the median and mean progression-free survival (PFS) periods were 246 and 383 days, respectively. The prognostic factors that were significantly related to better tumor control were prescription radiation dose of 16 Gy (p=0.000) and tumor volume less than both 4 mL (p=0.001) and 10 mL at the repeat SRS (p=0.008). The overall survival (OS) periods for all 114 patients after repeat SRS varied from 1 to 56 months, and median and mean OS periods were 229 and 404 days after the repeat SRS, respectively. The main cause of death was systemic problems including pulmonary dysfunction (n=58, 51%), and the identified direct or suspected brain-related death rate was around 20%. **CONCLUSION:** The tumor control following repeat SRS for locally recurring metastatic brain tumors after a previous SRS is relatively lower than that for primary SRS. However, both low tumor volume and high prescription radiation dose were significantly related to the tumor control following repeat SRS for these tumors after previous SRS, which is a general understanding of primary SRS for metastatic brain tumors.

[110] Absolute CBV for the differentiation of recurrence and radionecrosis of brain metastases after gamma knife radiotherapy: a comparison with relative CBV.

Clinical radiology. 2018;73(8):758.e1-758.e7

Wang B, Zhao B, Zhang Y, Ge M, Zhao P, Na Sun, Li C, Pang Q, Xu S, Liu Y
PMID: 29764622 DOI: 10.1016/j.crad.2018.04.006

AIM: To investigate the efficiency of absolute cerebral blood volume (CBV) in the differentiation of tumour recurrence (TR) and radionecrosis (RN) in brain metastases (BM) and to evaluate the performance of absolute CBV compared to relative CBV (rCBV). **MATERIALS AND METHODS:** Between March 2015 and June 2017, 46 patients with BM underwent quantitative dynamic susceptibility contrast perfusion-weighted imaging (DSC-PWI) because new enhancement had been demonstrated in irradiated lesions after gamma knife radiotherapy. The patients were assigned to either the TR group or RN group on the basis of MR perfusion follow-up or histopathological outcome. Absolute CBV of lesions (CBV_{lesion}) and contralateral normal appearing white matter (CBV_{NAWM}) in both groups were obtained. Mean rCBV were calculated as CBV_{lesion}/CBV_{NAWM}, which was equal to rCBV using traditional DSC-PWI. **RESULTS:** CBV_{lesion} of TR alone was significantly higher than the other parameters in both groups (p<0.001, separately). CBV_{lesion} had smaller interobserver difference than CBV_{NAWM} and rCBV (p<0.001, separately). Although CBV_{lesion} significantly correlated with rCBV (r=0.914, p<0.001) and both had a similar specificity (96%) in differential diagnosis, CBV_{lesion} had a higher sensitivity (96.9% versus 90.9%) to predict the treatment outcome. The best cut-off value of CBV_{lesion} was 21.8 ml/100 g. **CONCLUSION:** Quantitative DSC-PWI is a powerful method for the assessment of radiosurgically treated brain metastases. Absolute CBV has higher diagnostic efficiency than rCBV, which enables an absolute quantification of the regional CBV and prediction

of tumour response. These advantages promote the intra- and inter-patient quantitative image comparison across different institutions.

[111] Long-Term Survivorship Following Stereotactic Radiosurgery Alone for Brain Metastases: Risk of Intracranial Failure and Implications for Surveillance and Counseling.

Neurosurgery. 2018;83(2):203-209

Gogineni E, Vargo JA, Glaser SM, Flickinger JC, Burton SA, Engh JA, Amankulor NM, Beriwal S, Quinn AE, Ozhasoglu C, Heron DE
PMID: 28945873 DOI: 10.1093/neuros/nyx376

BACKGROUND: Historically, survival for even highly select cohorts of brain metastasis patients selected for SRS alone is <2 yr; thus, limited literature on risks of recurrence exists beyond 2 yr. **OBJECTIVE:** To investigate the possibility that for subsets of patients the risk of intracranial failure beyond 2 yr is less than the commonly quoted 50% to 60%, wherein less frequent screening may be appropriate. **METHODS:** As a part of our institutional radiosurgery database, we identified 132 patients treated initially with stereotactic radiosurgery (SRS) alone (+/- pre-SRS surgical resection) with at least 2 yr of survival and follow-up from SRS. Primary study endpoints were rates of actuarial intracranial progression beyond 2 yr, calculated using the Kaplan-Meier and Cox regression methods. **RESULTS:** The median follow-up from the first course of SRS was 3.5 yr. Significant predictors of intracranial failure beyond 2 yr included intracranial failure before 2 yr (52% vs 25%, P < .01) and total SRS tumor volume >=5 cc (51% vs 25%, P < .01). On parsimonious multivariate analysis, failure before 2 yr (HR = 2.2, 95% CI: 1.2-4.3, P = .01) and total SRS tumor volume >=5 cc (HR = 2.3, 95% CI: 1.2-4.3, P = .01) remained significant predictors of intracranial relapse beyond 2 yr. **CONCLUSION:** Relapse rates beyond 2 yr following SRS alone for brain metastases are low in patients who do not suffer intracranial relapse within the first 2 yr and with low-volume brain metastases, supporting a practice of less frequent screening beyond 2 yr. For remaining patients, frequent (every 3-4 mo) screening remains prudent, as the risk of intracranial failure after 2 yr remains high.

[112] Impact of 2-staged stereotactic radiosurgery for treatment of brain metastases >= 2 cm.

Journal of neurosurgery. 2018;129(2):366-382

Angelov L, Mohammadi AM, Bennett EE, Abbassy M, Elson P, Chao ST, Montgomery JS, Habboub G, Vogelbaum MA, Suh JH, Murphy ES, Ahluwalia MS, Nagel SJ, Barnett GH
PMID: 28937324 DOI: 10.3171/2017.3.JNS162532

OBJECTIVE: Stereotactic radiosurgery (SRS) is the primary modality for treating brain metastases. However, effective radiosurgical control of brain metastases >= 2 cm in maximum diameter remains challenging and is associated with suboptimal local control (LC) rates of 37%-62% and an increased risk of treatment-related toxicity. To enhance LC while limiting adverse effects (AEs) of radiation in these patients, a dose-dense treatment regimen using 2-staged SRS (2-SSRS) was used. The objective of this study was to evaluate the efficacy and toxicity of this treatment strategy. **METHODS:** Fifty-four patients (with 63 brain metastases >= 2 cm) treated with 2-SSRS were evaluated as part of an institutional review board-approved retrospective review. Volumetric measurements at first-stage stereotactic radiosurgery (first SSRS) and second-stage SRS (second SSRS) treatments and on follow-up imaging studies were determined. In addition to patient demographic data and tumor characteristics, the study evaluated 3 primary outcomes: 1) response at first follow-up MRI, 2) time to local progression (TTP), and 3) overall survival (OS) with 2-SSRS. Response was analyzed using methods for binary data, TTP was analyzed using competing-risks methods to account for patients who died without disease progression, and OS was analyzed using conventional time-to-event methods. When needed, analyses accounted for multiple lesions in the same patient. **RESULTS:** Among 54 patients, 46 (85%) had 1 brain metastasis treated with 2-SSRS, 7 patients (13%) had 2 brain metastases concurrently treated with 2-SSRS, and 1 patient underwent 2-SSRS for 3 concurrent brain metastases >= 2 cm. The median age was 63 years (range 23-83

years), 23 patients (43%) had non-small cell lung cancer, and 14 patients (26%) had radioresistant tumors (renal or melanoma). The median doses at first and second SSRS were 15 Gy (range 12-18 Gy) and 15 Gy (range 12-15 Gy), respectively. The median duration between stages was 34 days, and median tumor volumes at the first and second SSRS were 10.5 cm³ (range 2.4-31.3 cm³) and 7.0 cm³ (range 1.0-29.7 cm³). Three-month follow-up imaging results were available for 43 lesions; the median volume was 4.0 cm³ (range 0.1-23.1 cm³). The median change in volume compared with baseline was a decrease of 54.9% (range -98.2% to 66.1%; $p < 0.001$). Overall, 9 lesions (14.3%) demonstrated local progression, with a median of 5.2 months (range 1.3-7.4 months), and 7 (11.1%) demonstrated AEs (6.4% Grade 1 and 2 toxicity; 4.8% Grade 3). The estimated cumulative incidence of local progression at 6 months was 12% +/- 4%, corresponding to an LC rate of 88%. Shorter TTP was associated with greater tumor volume at baseline ($p = 0.01$) and smaller absolute ($p = 0.006$) and relative ($p = 0.05$) decreases in tumor volume from baseline to second SSRS. Estimated OS rates at 6 and 12 months were 65% +/- 7% and 49% +/- 8%, respectively. **CONCLUSIONS:** 2-SSRS is an effective treatment modality that resulted in significant reduction of brain metastases ≥ 2 cm, with excellent 3-month (95%) and 6-month (88%) LC rates and an overall AE rate of 11%. Prospective studies with larger cohorts and longer follow-up are necessary to assess the durability and toxicities of 2-SSRS.

[113] Early imaging radioresponsiveness of melanoma brain metastases as a predictor of patient prognosis.

Journal of neurosurgery. 2018;129(2):354-365

Zubatkina I, Ivanov P

PMID: 28841116 DOI: 10.3171/2017.1.JNS162075

OBJECTIVE: The aim of this study was to analyze the early radiological response of melanoma brain metastases to single high-dose irradiation and to reveal possible correlations between tumor radioresponsiveness and patient clinical outcomes. **METHODS:** The authors performed a retrospective analysis of the medical data for all patients with melanoma brain metastases who had undergone Gamma Knife radiosurgery (GKRS) and follow-up MRI examinations with standard protocols at regular 2- to 3-month intervals. Volumetric measurements of the metastases on pretreatment and initial posttreatment images were performed to assess the rate of early radiological response. Patients were divided into 2 groups according to the rate of response, and overall survival, local control, and the appearance of new metastases in the brain were compared in these groups using the long-rank test. Univariate and multivariate analyses were performed to identify predictors of clinical outcomes. **RESULTS:** After retrospective analysis of 298 melanoma brain metastases in 78 patients, the authors determined that early radiological responses of these metastases to GKRS differ considerably and can be divided into 2 distinct groups. One group of tumors underwent rapid shrinkage after radiosurgery, whereas the other showed minor fluctuations in size (rapid- and slow-response groups, respectively). Median survival for patients with a slow response was 15.2 months compared with 6.3 months for those with a rapid response ($p < 0.0001$). In the multivariate analysis, improved overall survival was associated with a slow response to radiosurgery ($p < 0.0001$), stable systemic disease ($p = 0.001$), and a higher Karnofsky Performance Scale score ($p = 0.001$). Stratification by Recursive Partitioning Analysis, score index for radiosurgery, and diagnosis-specific Graded Prognostic Assessment classes further confirmed the difference in overall survival for patients with a slow versus rapid radiation response. Local recurrence was observed in 11% of patients with a rapid response and in 6% of patients with a slow response, at a median of more than 8 months after radiosurgery. New brain metastases were diagnosed in 67% of patients with a slow response at a median of 8.6 months after radiosurgery and in 82% of patients with a rapid response at a considerably earlier median time of 2.7 months. In the multivariate analysis, a longer time to the development of new brain metastases was associated with a slow response ($p = 0.012$), stable systemic disease ($p = 0.034$), and a single brain metastasis ($p = 0.030$). **CONCLUSIONS:** Melanoma brain metastases show different early radioresponsiveness to radiosurgery. Rapid shrinkage of brain metastases is associated with poor patient prognosis, which may indicate more aggressive biological behavior of this tumor phenotype.

[114] Effect of Targeted Therapies on Prognostic Factors, Patterns of Care, and Survival in Patients With Renal Cell Carcinoma and Brain Metastases.

International journal of radiation oncology, biology, physics. 2018;101(4):845-853
Sperduto PW, Deegan BJ, Li J, Jethwa KR, Brown PD, Lockney N, Beal K, Rana NG, Attia A, Tseng CL, Sahgal A, Shanley R, Sperduto WA, Lou E, Zahra A, Buatti JM, Yu JB, Chiang V, Molitoris JK, Masucci L, Roberge D, Shi DD, Shih HA, Olson A, Kirkpatrick JP, Braunstein S, Sneed P, Mehta MP
PMID: 29976497 DOI: 10.1016/j.ijrobp.2018.04.006

PURPOSE: To identify prognostic factors, define evolving patterns of care, and the effect of targeted therapies in a larger contemporary cohort of renal cell carcinoma (RCC) patients with new brain metastases (BM). **METHODS AND MATERIALS:** A multi-institutional retrospective institutional review board-approved database of 711 RCC patients with new BM diagnosed from January 1, 2006, to December 31, 2015, was created. Clinical parameters and treatment were correlated with median survival and time from primary diagnosis to BM. Multivariable analyses were performed. **RESULTS:** The median survival for the prior/present cohorts was 9.6/12 months, respectively ($P < .01$). Four prognostic factors (Karnofsky performance status, extracranial metastases, number of BM, and hemoglobin b) were significant for survival after the diagnosis of BM. Of the 6 drug types studied, only cytokine use after BM was associated with improved survival. The use of whole-brain radiation therapy declined from 50% to 22%, and the use of stereotactic radiosurgery alone increased from 46% to 58%. Nonneurologic causes of death were twice as common as neurologic causes. **CONCLUSIONS:** Additional prognostic factors refine prognostication in this larger contemporary cohort. Patterns of care have changed, and survival of RCC patients with BM has improved over time. The reasons for this improvement in survival remain unknown but may relate to more aggressive use of local brain metastasis therapy and a wider array of systemic treatment options for those patients with progressive extracranial tumor.

[115] Evaluation of Prognostic Factors for Early Mortality After Stereotactic Radiosurgery for Brain Metastases: a Single Institutional Retrospective Review.

Neurosurgery. 2018;83(1):128-136

Bennett EE, Vogelbaum MA, Barnett GH, Angelov L, Chao S, Murphy E, Yu J, Suh JH, Elson P, Stevens GHJ, Mohammadi AM

PMID: 28673040 DOI: 10.1093/neuros/nyx346

BACKGROUND: Stereotactic radiosurgery (SRS) is used commonly for patients with brain metastases (BM) to improve intracranial disease control. However, survival of these patients is often dictated by their systemic disease course. The value of SRS becomes less clear in patients with anticipated short survival. **OBJECTIVE:** To evaluate prognostic factors, which may predict early death (within 90 d) after SRS. **METHODS:** A total of 1427 patients with BM were treated with SRS at our institution (2000-2012). There were 1385 cases included in this study; 1057 patients underwent upfront SRS and 328 underwent salvage SRS. The primary endpoint of the study was all-cause mortality within 90 d after first SRS. Multivariate analyses were performed to develop prognostic indices. **RESULTS:** Two hundred sixty-six patients (19%, 95% confidence interval 17%-21%) died within 90 d after SRS. Multivariate analysis of upfront SRS patients showed that Karnofsky Performance Status, primary tumor type, extracranial metastases, age at SRS, boost treatment, total tumor volume, prior surgery, and interval from primary to BM were independent prognostic factors for 90-d mortality. The first 4 factors were also independent predictors in patients treated with salvage SRS. Based on these factors, an index was defined for each group that categorized patients into 3 and 2 prognostic groups, respectively. Ninety-day mortality was 5% to 7% in the most favorable cohort and 36% to 39% in the least favorable. **CONCLUSION:** Indices based on readily available patient, clinical, and treatment factors that are highly predictive of early death in patients treated with upfront or salvage SRS can be calculated and used to define well-separated prognostic groups.

[116] Evaluation of new lesions and symptoms after gamma knife radiosurgery for brain metastases: a retrospective cohort study.

Acta neurochirurgica. 2018;160(7):1461-1471

Nakazaki K, Nishigaki M

PMID: 29633031 DOI: 10.1007/s00701-018-3524-x

BACKGROUND: Symptomatic new lesions that appear after gamma knife radiosurgery (GKRS) for brain metastases have not been thoroughly described. **METHODS:** Among 238 patients who underwent a single session of GKRS without whole-brain radiotherapy or surgery for brain metastases between 2009 and 2014, a total of 165 (69.3%) patients underwent follow-up magnetic resonance imaging (MRI). Their electrical health records were reviewed retrospectively. The median age was 68 years, and 62.4% patients were men. The median number of brain metastases was 2. The most frequent primary organ site was the lung (71.5%). Then, we evaluated predictors for the symptoms of new lesions. **RESULTS:** New lesions and leptomeningeal dissemination were observed in 101 (61.2%) and 23 (14.2%) patients, respectively. The median number of new lesions was 2; moreover, 20 of 101 patients (19.8%) with new lesions had tumours with the largest diameters of > 1 cm. Among 101 patients with new lesions, 13 were symptomatic (12.9%). Patients with larger new lesions (> 1 cm of the largest diameter) experienced symptoms more frequently (odds ratio 7.6, $P < 0.01$). Symptoms resolved after salvage GKRS in seven of 11 patients who abided by the recommended follow-up MRI schedule. No significant risk factors were found for symptoms of new lesions. **CONCLUSIONS:** The incidence of symptomatic new lesions that appeared after GKRS was low, and more than half of the patients showed improvements in their symptoms after salvage GKRS. However, careful MRI-based assessments and salvage GKRS are critical for the quality of life.

[117] Staged Stereotactic Radiosurgery for Large Brain Metastases: Local Control and Clinical Outcomes of a One-Two Punch Technique.

Neurosurgery. 2018;83(1):114-121

Dohm A, McTyre ER, Okoukoni C, Henson A, Cramer CK, LeCompte MC, Ruiz J, Munley MT, Qasem S, Lo HW, Xing F, Watabe K, Laxton AW, Tatter SB, Chan MD
PMID: 28973432 DOI: 10.1093/neuros/nyx355

BACKGROUND: Treatment options are limited for large, unresectable brain metastases. **OBJECTIVE:** To report a single institution series of staged stereotactic radiosurgery (SRS) that allows for tumor response between treatments in order to optimize the therapeutic ratio. **METHODS:** Patients were treated with staged SRS separated by 1 mo with a median dose at first SRS of 15 Gy (range 10-21 Gy) and a median dose at second SRS of 14 Gy (range 10-18 Gy). Overall survival was evaluated using the Kaplan-Meier method. Cumulative incidences were estimated for neurological death, radiation necrosis, local failure (marginal or central), and distant brain failure. Absolute cumulative dose-volume histogram was created for each treated lesion. Logistic regression and competing risks regression were performed for each discrete dose received by a certain volume. **RESULTS:** Thirty-three patients with 39 lesions were treated with staged radiosurgery. Overall survival at 6 and 12 mo was 65.0% and 60.0%, respectively. Cumulative incidence of local failure at 6 and 12 mo was 3.2% and 13.3%, respectively. Of the patients who received staged therapy, 4 of 33 experienced local failure. Radiation necrosis was seen in 4 of 39 lesions. Two of 33 patients experienced a Radiation Therapy Oncology Group toxicity grade > 2 (2 patients had grade 4 toxicities). Dosimetric analysis revealed that dose (Gy) received by volume of brain (ie, VDose(Gy)) was associated with radiation necrosis, including the range V44.5Gy to V87.8Gy. **CONCLUSION:** Staged radiosurgery is a safe and effective option for large, unresectable brain metastases. Prospective studies are required to validate the findings in this study.

[118] Predictors of quality of life and survival following Gamma Knife surgery for lung cancer brain metastases: a prospective study.

Journal of neurosurgery. 2018;129(1):71-83

Bragstad S, Flatebo M, Natvig GK, Eide GE, Skeie GO, Behbahani M, Pedersen PH, Enger PO, Skeie BS

PMID: 28820304 DOI: 10.3171/2017.2.JNS161659

OBJECTIVE: Lung cancer (LC) patients who develop brain metastases (BMs) have a poor prognosis. Estimations of survival and risk of treatment-related deterioration in quality of life (QOL) are important when deciding on treatment. Although we know of several prognostic factors for LC patients with BMs, the role of QOL has not been established. Authors of this study set out to evaluate changes in QOL following Gamma Knife surgery (GKS) for BMs in LC patients and QOL as a prognostic factor for survival. **METHODS:** Forty-four of 48 consecutive LC patients with BMs underwent GKS in the period from May 2010 to September 2011, and their QOL was prospectively assessed before and 1, 3, 6, 9, and 12 months after GKS by using the Functional Assessment of Cancer Therapy-Brain (FACT-BR) questionnaire. A mixed linear regression model was used to identify potential predictive factors for QOL and to assess the effect of GKS and the disease course on QOL at follow-up. **RESULTS:** Mean QOL as measured by the brain cancer subscale (BRCS) of the FACT-BR remained stable from baseline (score 53.0) up to 12 months post-GKS (57.1; $p = 0.624$). The BRCS score improved for 32 patients (72.3%) with a total BM volume ≤ 5 cm³. Mean improvement in these patients was 0.45 points each month of follow-up, compared to a decline of 0.50 points each month despite GKS treatment in patients with BM volumes > 5 cm³ ($p = 0.04$). Asymptomatic BMs ($p = 0.01$), a lower recursive partitioning analysis (RPA) classification ($p = 0.04$), and a higher Karnofsky Performance Scale (KPS) score ($p < 0.01$) at baseline were predictors for a high, stable QOL after GKS. After multivariate analysis, a high KPS score ($p < 0.01$) remained the only positive predictor of a high, stable QOL post-GKS. Median survival post-GKS was 5.6 months (95% CI 1.0-10.3). A higher BRCS score ($p = 0.01$), higher KPS score ($p = 0.01$), female sex ($p = 0.01$), and the absence of liver ($p = 0.02$), adrenal ($p = 0.02$), and bone metastases ($p = 0.03$) predicted longer survival in unadjusted models. However, in multivariate analyses, a higher BRCS score ($p < 0.01$), female sex ($p = 0.01$), and the absence of bone metastases ($p = 0.02$) at GKS remained significant predictors. Finally, the BRCS score's predictive value for survival was compared with the values for the variables behind well-known prognostic indices: age, KPS score, extracranial disease status, and number and volume of BMs. Both BRCS score ($p = 0.01$) and BM volume ($p = 0.05$) remained significant predictors for survival in the final model. **CONCLUSIONS:** Patient-reported QOL according to the BRCS is a predictor of survival in patients with BMs and may be helpful in deciding on the optimal treatment. Gamma Knife surgery is a safe and effective therapeutic modality that improves QOL for LC patients with a BM volume ≤ 5 cm³ at treatment. Careful follow-up and salvage therapy on demand seem to prevent worsening of QOL due to relapse of BMs.

[119] Melanoma brain metastasis: the impact of stereotactic radiosurgery, BRAF mutational status, and targeted and/or immune-based therapies on treatment outcome.

Journal of neurosurgery. 2018;129(1):50-59

Kotecha R, Miller JA, Venur VA, Mohammadi AM, Chao ST, Suh JH, Barnett GH, Murphy ES, Funchain P, Yu JS, Vogelbaum MA, Angelov L, Ahluwalia MS
PMID: 28799876 DOI: 10.3171/2017.1.JNS162797

OBJECTIVE: The goal of this study was to investigate the impact of stereotactic radiosurgery (SRS), BRAF status, and targeted and immune-based therapies on the recurrence patterns and factors associated with overall survival (OS) among patients with melanoma brain metastasis (MBM). **METHODS:** A total of 366 patients were treated for 1336 MBMs; a lesion-based analysis was performed on 793 SRS lesions. The BRAF status was available for 78 patients: 35 had BRAF (mut) and 43 had BRAF wild-type (BRAF-WT) lesions. The Kaplan-Meier method evaluated unadjusted OS; cumulative incidence analysis determined the incidences of local failure (LF), distant failure, and radiation necrosis (RN), with death as a competing risk. **RESULTS:** The 12-month OS was 24% (95% CI 20%-29%). On multivariate analysis, younger age, lack of extracranial metastases, better Karnofsky Performance Status score, and fewer MBMs, as well as treatment with BRAF inhibitors (BRAFi), anti-PD-1/CTLA-4 therapy, or cytokine therapy were significantly associated with OS. For patients who underwent SRS, the 12-month

LF rate was lower among those with BRAF (mut) lesions (6%, 95% CI 2%-11%) compared with those with BRAF-WT lesions (22%, 95% CI 13%-32%; $p < 0.01$). The 12-month LF rates among lesions treated with BRAFi and PD-1/CTLA-4 agents were 1% (95% CI 1%-4%) and 7% (95% CI 1%-13%), respectively. On multivariate analysis, BRAF inhibition within 30 days of SRS was protective against LF (HR 0.08, 95% CI 0.01-0.55; $p = 0.01$). The 12-month rates of RN were low among lesions treated with BRAFi (0%, 95% CI 0%-0%), PD-1/CTLA-4 inhibitors (2%, 95% CI 1%-5%), and cytokine therapies (6%, 95% CI 1%-13%). **CONCLUSIONS:** Prognostic schema should incorporate BRAFi or immunotherapy status and use of targeted therapies. Treatment with a BRAF inhibitor within 4 weeks of SRS improves local control without an increased risk of RN.

[120] Predictors for a further local in-brain progression after re-craniotomy of locally recurrent cerebral metastases.

Neurosurgical review. 2018;41(3):813-823

Kamp MA, Fischer I, Dibue-Adjei M, Munoz-Bendix C, Cornelius JF, Steiger HJ, Slotty PJ, Turowski B, Rapp M, Sabel M
PMID: 29260342 DOI: 10.1007/s10143-017-0931-z

Treatment of recurrent cerebral metastases is an emerging challenge due to the high local failure rate after surgery or radiosurgery and the improved prognosis of patients with malignancies. A total of 36 patients with 37 metastases who underwent surgery for a local in-brain progression of a cerebral metastasis after previous metastasectomy were retrospectively analyzed. Degree of surgical resection on an early postoperative MRI within 72 h after surgery was correlated with the local in-brain progression rate and overall survival. Complete surgical resection of locally recurrent cerebral metastases as confirmed by early postoperative MRI could only be achieved in 37.8%. Detection of residual tumor tissue on an early MRI following recurrent metastasis surgery correlated with further local in-brain progression when defining a significance level of $p = 0.05$ but not after Sidak or Bonferroni significance level correction for multiple testing: However, definite local tumor control could finally be achieved in 91.9% after adjuvant therapy. Overall survival after recurrent metastasectomy was significantly higher as predicted by diagnosis-specific graded prognostic assessment (12.9 +/- 2.3 vs. 8.4 +/- 0.7 months; $p < 0.0001$). However, our series involved a limited number of heterogeneous patients. A larger, prospective, and controlled study is required. Considering the adequate local tumor control achieved in the vast majority of patients, surgery of recurrent metastases may represent one option in a multi-modal treatment approach of patients suffering from locally recurrent cerebral metastases.

[121] The concept of rapid rescue radiosurgery in the acute management of critically located brain metastases: A retrospective short-term outcome analysis.

Surgical neurology international. 2018;9:218

Sinclair G, Benmakhlouf H, Brigui M, Maeurer M, Doodoo E
PMID: 30505620 DOI: 10.4103/sni.sni_480_17

BACKGROUND: Adaptive hypofractionated gamma knife radiosurgery has been used to treat brain metastases in the eloquent regions while limiting the risk of adverse radiation effect (ARE). Ablative responses might be achieved within days to weeks with the goal to preserve the neurological function. The application of this treatment modality in selected acute/subacute settings has been termed Rapid Rescue Radiosurgery (RRR) in our department. We report the expeditious effects of RRR during treatment and 4 weeks after treatment completion.

METHODS: In all, 34 patients with 40 brain metastases, each treated over a period of 7 days in three separate gamma knife radiosurgery sessions (GKRS 1-3) between November 2013 and August 2017, were retrospectively analyzed in terms of tumor volume reduction, salvage of organs at risk (OAR), and radiation induced toxicity under the period of treatment (GKRS 1-3 = one week) and at first follow-up magnetic resonance imaging (MRI) (4 weeks after GKRS 3). **RESULTS:** Mean tumor volume at GKRS 1 was 12.8 cm³. Mean peripheral doses at GKRS 1, GKRS 2, and GKRS 3 were 7.7 Gy, 8.1 Gy, and 8.4 Gy (range: 6.0-9.5 Gy) at the 35% to 50% isodose lines. In the surviving group at first follow-up ($n = 28$), mean tumor

volume reduction was - 10% at GKRS 3 (1 week) and - 48% four weeks after GKRS 3. There was no further clinical deterioration between GKRS 3 and first follow-up in 21 patients. Six patients died prior to first follow-up due to extracranial disease. No ARE was noticed/reported. **CONCLUSIONS:** In this study, RRR proved effective in terms of rapid tumor volume reduction, debulking, and preservation/rescue of neurological function.

[122] Gamma Knife Radiosurgery for Metastatic Brain Tumors from Malignant Melanomas: A Japanese Multi-Institutional Cooperative and Retrospective Cohort Study (JLGK1501).

Stereotactic and functional neurosurgery. 2018;96(3):162-171

Matsunaga S, Shuto T, Yamamoto M, Yomo S, Kondoh T, Kobayashi T, Sato M, Okamoto H, Serizawa T, Nagano O, Kenai H, Obara T, Iwai Y, Yasuda S, Hasegawa T, Kubo K, Shidoh S, Mori K, Hayashi M, Inoue A, Onoue S, Gondo M
PMID: 29969770 DOI: 10.1159/000489948

BACKGROUND: The incidences of metastatic brain tumors from malignant melanomas have increased and survival has been prolonged by novel molecular targeted agents and immunotherapy. However, malignant melanomas are uncommon in Asian populations. **OBJECTIVES:** We retrospectively analyzed treatment efficacy and identified prognostic factors impacting tumor control and survival in Japanese melanoma patients with brain metastases treated with gamma knife radiosurgery (GKRS). **METHODS:** We retrospectively reviewed the medical records of 177 patients with 1,500 tumors who underwent GKRS for brain metastases from malignant melanomas. This study was conducted by the Japanese Leksell Gamma Knife Society (JLGK1501). **RESULTS:** Six and 12 months after GKRS, the cumulative incidences of local tumor recurrence were 9.2 and 13.8%. Intratumoral hemorrhage ($p < 0.0001$) and larger tumor volume ($p = 0.001$) in GKRS were associated with significantly poorer local control outcomes. The use of immune checkpoint inhibitors before GKRS was significantly associated with symptomatic adverse events ($p = 0.037$). The median overall survival time after the initial GKRS was 7.3 months. Lower Karnofsky performance status scores ($p = 0.016$), uncontrolled primary cancer ($p < 0.0001$), and multiple brain metastases ($p = 0.014$) significantly influenced unfavorable overall survival outcomes. The cumulative incidences of neurological death 6 and 12 months after GKRS were 9.7 and 17.4%, those of neurological deterioration were 14.2 and 19.6%, and those of new tumor appearance were 34.5 and 40.5%. **CONCLUSIONS:** The results of the present multicenter study suggest that GKRS is a relatively effective and safe modality for control of tumor progression in Japanese patients with brain metastases from malignant melanomas.

[123] Repeated in-field radiosurgery for locally recurrent brain metastases: Feasibility, results and survival in a heavily treated patient cohort.

PloS one. 2018;13(6):e0198692

Balermpas P, Stera S, Muller von der Grun J, Loutfi-Krauss B, Forster MT, Wagner M, Keller C, Rodel C, Seifert V, Blanck O, Wolff R
PMID: 29874299 DOI: 10.1371/journal.pone.0198692

PURPOSE: Stereotactic radiosurgery (SRS) is an established primary treatment for newly diagnosed brain metastases with high local control rates. However, data about local re-irradiation in case of local failure after SRS (re-SRS) are rare. We evaluated the feasibility, efficacy and patient selection characteristics in treating locally recurrent metastases with a second course of SRS. **METHODS:** We retrospectively evaluated patients with brain metastases treated with re-SRS for local tumor progression between 2011 and 2017. Patient and treatment characteristics as well as rates of tumor control, survival and toxicity were analyzed. **RESULTS:** Overall, 32 locally recurrent brain metastases in 31 patients were irradiated with re-SRS. Median age at re-SRS was 64.9 years. The primary histology was breast cancer and non-small-cellular lung cancer (NSCLC) in respectively 10 cases (31.3%), in 5 cases malignant melanoma (15.6%). In the first SRS-course 19 metastases (59.4%) and in the re-SRS-course 29 metastases (90.6%) were treated with CyberKnife(R) and the others with Gamma Knife. Median planning target volume (PTV) for re-SRS was 2.5 cm³ (range, 0.1-37.5 cm³) and

median dose prescribed to the PTV was 19 Gy (range, 12-28 Gy) in 1-5 fractions to the median 69% isodose (range, 53-80%). The 1-year overall survival rate was 61.7% and the 1-year local control rate was 79.5%. The overall rate of radiological radio-necrosis was 16.1% and four patients (12.9%) experienced grade ≥ 3 toxicities. **CONCLUSIONS:** A second course of SRS for locally recurrent brain metastases after prior local SRS appears to be feasible with acceptable toxicity and can be considered as salvage treatment option for selected patients with high performance status. Furthermore, this is the first study utilizing robotic radiosurgery for this indication, as an additional option for frameless fractionated treatment.

[124] Potential prognostic markers for survival and neurologic death in patients with breast cancer brain metastases who receive upfront SRS alone.

Journal of radiosurgery and SBRT. 2018;5(4):277-283

Shenker RF, Hughes RT, McTyre ER, Lanier C, Lo HW, Metheny-Barlow L, Su J, Thomas A, Brown DR, Avery T, Pasche B, Cramer CK, Laxton AW, Tatter SB, Watabe K, Chan MD

PMID: 30538888 DOI:

PURPOSE/OBJECTIVES: Stereotactic radiosurgery (SRS) is used as a treatment option for breast cancer brain metastases. It is unclear what factors predict neurologic death for these patients. **MATERIALS/METHODS:** A total of 128 patients with breast cancer brain metastases were treated with upfront SRS alone in this study. Survival was estimated using the Kaplan-Meier method. Clinicopathologic factors evaluated included age, ER/PR status, Her2 status, numbers of brain metastases treated, minimum SRS dose, disease-specific GPA, extracranial disease status and systemic disease burden. **RESULTS:** ER or PR positivity was associated with a trend towards decreased neurologic death (subdistribution hazard ratio (sHR) = 0.54, $p=0.06$). Factors associated with non-neurologic death include extracranial disease status (sHR = 2.02, $p=0.02$) and dose (sHR = 1.11, $p=0.02$); Her2-positivity was associated with reduced hazard of non-neurologic death (sHR 0.52, $p=0.05$). **CONCLUSIONS:** ER/PR positivity was associated with a trend towards less neurologic death. HER2 positivity was associated with a trend towards less non-neurologic death.

[125] Postcontrast T1 Mapping for Differential Diagnosis of Recurrence and Radionecrosis after Gamma Knife Radiosurgery for Brain Metastasis.

AJNR. American journal of neuroradiology. 2018;39(6):1025-1031

Wang B, Zhang Y, Zhao B, Zhao P, Ge M, Gao M, Ding F, Xu S, Liu Y

PMID: 29724761 DOI: 10.3174/ajnr.A5643

BACKGROUND AND PURPOSE: The differential diagnosis of radionecrosis and tumor recurrence in brain metastases is challenging. We investigated the diagnostic efficiency of postcontrast T1 mapping in solving this problem. **MATERIALS AND METHODS:** Between March 2016 and June 2017, fifty-six patients with brain metastases who underwent contrast-enhanced cerebral T1 mapping were recruited for this prospective study. The findings revealed new enhancement after gamma knife radiosurgery. The subjects were assigned to radionecrosis and recurrence groups based on follow-up (median, 11.5 months) and histopathologic results. T1 values of lesions 5 (T15min) and 60 (T160min) minutes after administration of contrast agent and their difference (T1differ) were compared between the 2 groups with the 2-tailed Mann-Whitney U test. Receiver operating characteristic curves were used to determine the optimum cutoff values for differential diagnosis. **RESULTS:** There were significant differences between the 2 groups in T15min, T160min, and T1differ values ($P = .012$, $P = .004$, and $P < .001$, respectively). Relative to T15min and T160min, T1differ exhibited greater sensitivity and specificity ($P < .001$, respectively) in identifying radionecrosis. The optimum T1differ value for differential diagnosis was 71.1 ms (area under the curve = 0.97; 95% CI, 0.93-1.00), with sensitivity and specificity of 81.5% and 96.5%, respectively. **CONCLUSIONS:** Postcontrast T1 mapping is optimal for the differential diagnosis of radionecrosis and tumor recurrence. Among T1 parameters, T1differ is the most powerful parameter for differential diagnosis. Advantages in terms of quantitative analysis and high resolution portend the wide use of postcontrast T1 mapping in the future.

[126] Validation of the Chowdhury overall survival score in patients with melanoma brain metastasis treated with Gamma Knife Radiosurgery.

Journal of neuro-oncology. 2018;138(2):391-399

Rodenburg RJ, Hanssens PE, Ho VKY, Beerepoot LV

PMID: 29470692 DOI: 10.1007/s11060-018-2808-6

Melanoma brain metastases (MBM) are common in patients with stage IV disease. For Gamma Knife radiosurgery (GKRS) on MBM, risk scores such as RPA and melanoma-GPA aid to identify prognostic subgroups. This study aimed to validate the overall survival (OS) risk score developed by Chowdhury et al. in our center's patient cohort. A total of 104 MBM patients were treated with GKRS between 1/1/2002 and 31/12/2014 in our institution. Patients were categorized according to RPA, melanoma-GPA and Chowdhury OS score. The Kaplan-Meier method was used to estimate overall survival, and predicted survival probabilities were calculated for calibration. Cox proportional hazards regressions were performed to identify additional risk factors. Overall, median follow-up time was 80 months, while median OS (mOS) after GKRS was 6 months. Stratified according to the Chowdhury OS score, mOS in the high, medium and low risk group was 3.4, 7.1, and 10.0 months, respectively. The addition of other patient or disease characteristics to the Chowdhury OS model did not improve its performance. The C-index of the melanoma-GPA was 0.46 while the Chowdhury OS had an index of 0.67. In comparison with the RPA and melanoma-GPA, the Chowdhury OS score more accurately distinguished between separate risk groups among patients with MBM treated with GKRS. Contrary to the original study by Chowdhury, follow-up time was sufficient here for the low-risk group to reach the mOS time of 10 months.

[127] Laser ablation after stereotactic radiosurgery: a multicenter prospective study in patients with metastatic brain tumors and radiation necrosis.

Journal of neurosurgery. 2018;130(3):804-811

Ahluwalia M, Barnett GH, Deng D, Tatter SB, Laxton AW, Mohammadi AM, Leuthardt E, Chamoun R, Judy K, Asher A, Essig M, Dietrich J, Chiang VL

PMID: 29726782 DOI: 10.3171/2017.11.JNS171273

OBJECTIVE: Laser Ablation After Stereotactic Radiosurgery (LAASR) is a multicenter prospective study of laser interstitial thermal (LITT) ablation in patients with radiographic progression after stereotactic radiosurgery for brain metastases. **METHODS:** Patients with a Karnofsky Performance Scale (KPS) score ≥ 60 , an age > 18 years, and surgical eligibility were included in this study. The primary outcome was local progression-free survival (PFS) assessed using the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria. Secondary outcomes were overall survival (OS), procedure safety, neurocognitive function, and quality of life. **RESULTS:** Forty-two patients-19 with biopsy-proven radiation necrosis, 20 with recurrent tumor, and 3 with no diagnosis-were enrolled. The median age was 60 years, 64% of the subjects were female, and the median baseline KPS score was 85. Mean lesion volume was 6.4 cm³ (range 0.4-38.6 cm³). There was no significant difference in length of stay between the recurrent tumor and radiation necrosis patients (median 2.3 vs 1.7 days, respectively). Progression-free survival and OS rates were 74% (20/27) and 72%, respectively, at 26 weeks. Thirty percent of subjects were able to stop or reduce steroid usage by 12 weeks after surgery. Median KPS score, quality of life, and neurocognitive results did not change significantly for either group over the duration of survival. Adverse events were also similar for the two groups, with no significant difference in the overall event rate. There was a 12-week PFS and OS advantage for the radiation necrosis patients compared with the recurrent tumor or tumor progression patients. **CONCLUSIONS:** In this study, in which enrolled patients had few alternative options for salvage treatment, LITT ablation stabilized the KPS score, preserved quality of life and cognition, had a steroid-sparing effect, and was performed safely in the majority of cases.

[128] Survival of Patients With Multiple Intracranial Metastases Treated With Stereotactic Radiosurgery: Does the Number of Tumors Matter?

American journal of clinical oncology. 2018;41(5):425-431

Knoll MA, Oermann EK, Yang AI, Paydar I, Steinberger J, Collins B, Collins S, Ewend M, Kondziolka D

PMID: 27258677 DOI: 10.1097/COC.0000000000000299

BACKGROUND: Defining prognostic factors is a crucial initial step for determining the management of patients with brain metastases. Randomized trials assessing radiosurgery have commonly limited inclusion criteria to 1 to 4 brain metastases, in part due to multiple retrospective studies reporting on the number of brain metastases as a prognostic indicator. The present study reports on the survival of patients with 1 to 4 versus ≥ 5 brain metastases treated with radiosurgery. **METHODS:** We evaluated a retrospective multi-institutional database of 1523 brain metastases in 507 patients who were treated with radiosurgery (Gamma Knife or Cyberknife) between 2001 and 2014. A total of 243 patients were included in the analysis. Patients with 1 to 4 brain metastases were compared with patients with ≥ 5 brain metastases using a standard statistical analysis. Cox hazard regression was used to construct a multivariable model of overall survival (OS). To find covariates that best separate the data at each split, a machine learning technique Chi-squared Automated Interaction Detection tree was utilized. **RESULTS:** On Pearson correlation, systemic disease status, number of intracranial metastases, and overall burden of disease (number of major involved organ systems) were found to be highly correlated ($P < 0.001$). Patients with 1 to 4 metastases had a median OS of 10.8 months (95% confidence interval, 6.1-15.6 mo), compared with a median OS of 8.5 months (95% confidence interval, 4.4-12.6 mo) for patients with ≥ 5 metastases ($P = 0.143$). The actuarial 6 month local failure rate was 5% for patients with 1 to 4 metastases versus 3.2% for patients with ≥ 5 metastases ($P = 0.404$). There was a significant difference in systemic disease status between the 2 groups; 30% of patients had controlled systemic disease in the < 5 lesions group, versus 8% controlled systemic disease in the ≥ 5 lesions group ($P = 0.005$). Patients with 1 to 4 metastases did not have significantly improved OS in a multivariable model adjusting for systemic disease status, systemic extracranial metastases, and other key variables. The Chi-squared Automated Interaction Detection tree (machine learning technique) algorithm consistently identified performance status and systemic disease status as key to disease classification, but not intracranial metastases. **CONCLUSIONS:** Although the number of brain metastases has previously been accepted as an independent prognostic indicator, our multicenter analysis demonstrates that the number of intracranial metastases is highly correlated with overall disease burden and clinical status. Proper matching and controlling for these other determinants of survival demonstrates that the number of intracranial metastases alone is not an independent predictive factor, but rather a surrogate for other clinical factors.

[129] Impacts of EGFR-mutation status and EGFR-TKI on the efficacy of stereotactic radiosurgery for brain metastases from non-small cell lung adenocarcinoma: A retrospective analysis of 133 consecutive patients.

Lung cancer (Amsterdam, Netherlands). 2018;119:120-126

Yomo S, Oda K

PMID: 29656746 DOI: 10.1016/j.lungcan.2018.03.013

OBJECTIVES: Recent advances in target therapies have prolonged overall survival (OS) for patients with epidermal growth factor receptor (EGFR)-mutant lung cancer. The impact of EGFR mutations on stereotactic radiosurgery (SRS) for brain metastases (BM) has yet to be determined. The present study sought to evaluate the efficacy and limitations of SRS, administered with EGFR-tyrosine kinase inhibitors (TKI), for BM from EGFR-mutant lung adenocarcinoma. **MATERIALS AND METHODS:** This retrospective observational study analyzed data from patients with BM arising from EGFR-mutant lung adenocarcinoma who received upfront Gamma Knife SRS between December 2010 and April 2016. OS and distant and local intracranial disease control rates were calculated. The prognostic factors for each event were also determined. **RESULTS:** One hundred thirty-three consecutive patients (47 males/86 females) were eligible. The median

age was 69 years, and the median Karnofsky performance status (KPS) was 90. Sixty-six patients (50%) had no history of EGFR-TKI use at the time of SRS. EGFR-TKI were administered to 85% of EGFR-TKI naive patients after SRS. One- and 2-year OS rates were 74% and 52%, respectively. One- and 2-year distant BM recurrence rates (per patient) after SRS were 34% and 53%, respectively. One- and 2-year rates of local tumor control (per lesion) were 97% and 95%, respectively. Multivariate proportional hazards analyses showed that being EGFR-TKI naive was associated with longer OS (HR: 0.42, $P < 0.001$), a lower distant intracranial recurrence rate (HR: 0.61, $P = 0.037$) and a higher local tumor control rate (HR: 0.28, $P = 0.001$). **CONCLUSIONS:** The present study demonstrated the upfront SRS strategy to offer a minimally invasive and effective treatment option for EGFR-mutant lung adenocarcinoma patients with limited BM. EGFR-TKI naive patients were found to be a distinct subgroup for which a longer survival time and durable intracranial disease control can be expected.

[130] Identifying candidates for gamma knife radiosurgery among elderly patients with brain metastases.

Journal of neuro-oncology. 2018;137(3):559-565

Roh TH, Choi MS, You N, Jeong D, Jang AH, Seo MR, Lee SR, Kim SH

PMID: 29327172 DOI: 10.1007/s11060-018-2745-4

We investigated the outcomes of gamma knife radiosurgery (GKRS) for elderly patients (≥ 65 years) with brain metastases, and identified survival-associated factors. We retrospectively analyzed data from 115 patients treated with GKRS for 1-15 brain metastases. The median patient age was 72 years; most primary tumors were pulmonary ($n = 83$). The mean lesion volume was 2.1 +/- 4.8 mL. A mean dose of 19.3 Gy was delivered to the mean 63.9% isodose line. The median overall survival (OS) was 5.3 months (95% confidence interval [CI] 3.5-7.1). During follow-up (median, 5.1 months), 91 patients died of primary cancer progression while 1 died of unknown causes. The 6- and 12-month local control rates were 94.9 and 88.1%, respectively. On multivariate analysis, female sex ($p = 0.005$, hazard ratio [HR] 0.533, 95% CI 0.343-0.827) and a controlled primary tumor ($p < 0.001$, HR 0.328, 95% CI 0.180-0.596) were significantly favorable prognostic factors. Of non-small cell lung cancer patients with EGFR mutations, 76.5% were women ($p = 0.005$). The median OS of EGFR-mutant and EGFR-wildtype patients were 19.1 and 4.7 months, respectively ($p = 0.080$). Brain metastases < 3 mL showed better local control rates after GKRS ($p = 0.005$). GKRS produces favorable outcomes in women with brain metastases who are ≥ 65 years and have controlled primary tumors. Such patients are therefore suitable candidates for GKRS.

[131] Efficacy of adjuvant radiotherapy in the intracranial hemangiopericytoma.

Journal of neuro-oncology. 2018;137(3):567-573

Jeon SH, Park SH, Kim JW, Park CK, Paek SH, Kim IH

PMID: 29327171 DOI: 10.1007/s11060-018-2746-3

We retrospectively evaluated an efficacy of adjuvant radiotherapy (RT) in the intracranial hemangiopericytoma (HPC) and analyzed prognostic factors influencing treatment outcomes. Among 49 patients diagnosed as localized intracranial HPC between 1995 and 2016, 31 patients received adjuvant RT after surgery; 26 with fractionated RT and 5 with stereotactic radiosurgery using Gamma Knife. After gross total resection (GTR) ($n = 32$) and subtotal resection (STR) ($n = 17$), histopathological grade was confirmed to be grade II ($n = 9$) or grade III ($n = 40$). The median follow-up period was 50 months (range 3-216 months). The local recurrence was defined as intracranial relapse within 15 mm and regional recurrence as beyond 15 mm from the margin of surgical bed. The 10-year overall survival (OS) and progression-free survival (PFS) were 69.9 and 34.4%, respectively. The 10-year local, regional, and distant failure-free rates were 56.6, 88.2, and 73.3%, respectively. Local tumor control was better with GTR followed by RT than GTR alone ($p = 0.056$), while there was no difference in OS. Local tumor control and OS after STR plus RT were equivalent to those after GTR alone. There were no differences in distant metastasis-free survival (DMFS) among GTR plus RT, GTR alone, and STR plus RT. Tumor volume > 40 cm³ was associated with poor PFS ($p = 0.024$). The local tumor recurrence was reduced by

adjuvant RT after surgery. But OS or DMFS was not improved with adjuvant RT. PFS was better in the tumor with small volume at diagnosis.

[132] Postoperative radiosurgery for the treatment of metastatic brain tumor: Evaluation of local failure and leptomeningeal disease.

Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2018;49:48-55

Foreman PM, Jackson BE, Singh KP, Romeo AK, Guthrie BL, Fisher WS, Riley KO, Markert JM, Willey CD, Bredel M, Fiveash JB

PMID: 29248376 DOI: 10.1016/j.jocn.2017.12.009

In patients undergoing surgical resection of a metastatic brain tumor, whole brain radiation therapy reduces the risk of recurrence and neurologic death. Focal radiation has the potential to mitigate neurocognitive side effects. We present an institutional experience of postoperative radiosurgery for the treatment of brain metastases. A retrospective review of a prospectively maintained institutional radiosurgery database was performed for the years 2005-2015 identifying all adult patients treated with postoperative radiosurgery to the tumor bed. Primary endpoints include local recurrence and postoperative LMD. Kaplan-Meier curves and Cox regression were used to evaluate time to local recurrence and postoperative LMD. Ninety-one patients received adjuvant focal radiation for a brain metastasis. Median radiographic follow-up among patients who had not developed a local failure was 9 months. Of the 91 patients, 20 (22%) developed local recurrence and 32 (35%) experienced postoperative LMD. Freedom from local recurrence and LMD at 1 year was 84% and 69%, respectively. In multivariable models, predictors of local failure included the presence of more than one brain metastasis (HR=2.65, p=.04) with a preoperative tumor diameter of >3cm (HR=4.16, p=.06) trending toward significance. There was a trend to a higher risk of LMD with >1 tumor (HR 2.07, p=.06) and breast cancer (HR 2.37, p=.07). More than one metastasis is an independent predictor of local and leptomeningeal failure following postoperative radiosurgery. The high rate of LMD was likely related to the liberal definition of LMD to include focal dural recurrences.

[133] The growing importance of lesion volume as a prognostic factor in patients with multiple brain metastases treated with stereotactic radiosurgery.

Cancer medicine. 2018;7(3):757-764

Routman DM, Bian SX, Diao K, Liu JL, Yu C, Ye J, Zada G, Chang EL

PMID: 29441722 DOI: 10.1002/cam4.1352

Stereotactic Radiosurgery (SRS) is considered standard of care for patients with 1-3 brain metastases (BM). Recent observational studies have shown equivalent OS in patients with 5+ BM compared to those with 2-4, suggesting SRS alone may be appropriate in these patients. We aim to review outcomes of patients treated with SRS with 2-4 versus 5+ BM. This analysis included consecutive patients from 1994 to 2015 treated with SRS. Of 1017 patients, we excluded patients with a single BM and patients without adequate survival data, resulting in 391 patients. All risk factors were entered into univariate analysis using Cox proportional hazards model, and significant factors were entered into multivariate analysis (MVA). We additionally analyzed outcomes after excluding patients with prior surgery or whole-brain radiotherapy (WBRT). Median follow-up was 7.1 months. Median KPS was 90, mean age was 59, and most common histologies were melanoma and lung. Median tumor volume was 3.41 cc. Patients with 2-4 BM had a median OS of 8.1 months compared to 6.2 months for those with 5+ BM (P = 0.0136). On MVA, tumor volume, KPS, and histology remained significant for OS, whereas lesion number did not. Similar results were found when excluding patients with prior surgery or WBRT. Rather than lesion number, the strongest prognostic factors for patients undergoing SRS were tumor volume >10 cc, KPS, and histology. BM number may therefore not be the most important criterion for candidacy for SRS. Patients with 5 or more BM should be considered for SRS.

[134] Multi-institutional competing risks analysis of distant brain failure and salvage patterns after upfront radiosurgery without whole brain radiotherapy for brain metastasis.

Annals of oncology : official journal of the European Society for Medical Oncology. 2018;29(2):497-503

McTyre E, Ayala-Peacock D, Contessa J, Corso C, Chiang V, Chung C, Fiveash J, Ahluwalia M, Kotecha R, Chao S, Attia A, Henson A, Hepel J, Braunstein S, Chan M

PMID: 29161348 DOI: 10.1093/annonc/mdx740

BACKGROUND: In this study, we use a competing risks analysis to assess factors predictive of early-salvage whole brain radiotherapy (WBRT) and early death after upfront stereotactic radiosurgery (SRS) alone for brain metastases in an attempt to identify populations that benefit less from upfront SRS. **PATIENTS AND METHODS:** Patients from eight academic centers were treated with SRS for brain metastasis. Competing risks analysis was carried out for distant brain failure (DBF) versus death prior to DBF as well as for salvage SRS versus salvage WBRT versus death prior to salvage. Linear regression was used to determine predictors of the number of brain metastases at initial DBF (nDBF). **RESULTS:** A total of 2657 patients were treated with upfront SRS alone. Multivariate analysis (MVA) identified an increased hazard of DBF associated with increasing number of brain metastases (P < 0.001), lowest SRS dose received (P < 0.001), and melanoma histology (P < 0.001), while there was a decreased hazard of DBF associated with increasing age (P < 0.001), KPS < 70 (P < 0.001), and progressive systemic disease (P = 0.004). MVA for first salvage SRS versus WBRT versus death prior to salvage revealed an increased hazard of first salvage WBRT seen with increasing number of brain metastases (P < 0.001) and a decreased hazard with widespread systemic disease (P = 0.002) and increasing age (P < 0.001). Variables associated with nDBF included age (P = 0.02), systemic disease status (P = 0.03), melanoma histology (P = 0.05), and initial number of brain metastases (P < 0.001). **CONCLUSIONS:** Patients with a higher initial number of brain metastases were more likely to experience DBF, have a higher nDBF, and receive early-salvage WBRT, while patients who were older, had lower KPS, or had more systemic disease were more likely to experience death prior to DBF or salvage WBRT.

[135] Validation of the Disease-Specific GPA for Patients With 1 to 3 Synchronous Brain Metastases in Newly Diagnosed NSCLC.

Clinical lung cancer. 2018;19(1):e141-e147

Woody NM, Greer MD, Reddy CA, Videtic GMM, Chao ST, Murphy ES, Suh JH, Angelov L, Barnett GH, Vogelbaum MA, Stephens KL

PMID: 28739316 DOI: 10.1016/j.clcc.2017.06.011

BACKGROUND: The disease-specific graded prognostic assessment (DS-GPA) for brain metastases is a powerful prognostic tool but has not been validated for patients with synchronous brain metastases (SBM) in newly diagnosed non-small-cell lung cancer (NSCLC). **PATIENTS AND METHODS:** We identified patients with newly diagnosed NSCLC with 1 to 3 SBM treated with stereotactic radiosurgery (SRS) between 1997 and 2012. We included patients whose brain metastases were treated with SRS alone or combined SRS and whole-brain radiotherapy (WBRT). Patients were stratified according to NSCLC DS-GPA to evaluate the accuracy of survival estimates. **RESULTS:** One hundred sixty-four patients were treated with either SRS alone (n = 85; 52%) or SRS and WBRT (n = 79; 48%). Median overall survival (OS) stratified according to DS-GPA of 0 to 1, 1.5 to 2, 2.5 to 3, and 3.5 to 4 were 2.8, 6.7, 9.8, and 13.2 months, respectively, consistent with OS reported for brain metastases in NSCLC DS-GPA (3.0, 6.5, 11.3, and 14.8 months, respectively). No difference in median progression-free survival or OS was noted with combined use of SRS and WBRT: 6.0 versus 6.1 months (P = .81) and 8.5 versus 9.1 months (P = .093), respectively. In multivariable analysis, Karnofsky performance status (hazard ratio [HR], 0.98; P = .008), extracranial metastases (HR, 0.498; P = .0003), squamous histology (HR, 1.81; P = .02), and number of brain metastases (2 vs. 1; HR, 1.504; P = .04, and 3 vs. 1; HR, 1.66; P = .05) were significant predictors of OS. **CONCLUSION:** The DS-GPA accurately estimates the prognosis of patients with SBM in newly diagnosed NSCLC. Patients

with synchronous brain metastasis in newly diagnosed NSCLC should be carefully stratified for consideration of aggressive therapy.

[136] Comparison of prognostic indices in patients who undergo melanoma brain metastasis radiosurgery.

Journal of neurosurgery. 2018;128(1):14-22

Kano H, Morales-Restrepo A, Iyer A, Weiner GM, Mousavi SH, Kirkwood JM, Tarhini AA, Flickinger JC, Lunsford LD

PMID: 28106495 DOI: 10.3171/2016.9.JNS161011

OBJECTIVE: The goal of this study was to use 4 prognostic indices to compare survival times of patients who underwent Gamma Knife stereotactic radiosurgery (SRS) to treat melanoma brain metastases. **METHODS:** The authors analyzed 422 consecutive patients (1440 brain metastases) who underwent Gamma Knife SRS. The median total brain tumor volume was 4.7 cm³ (range 0.3-69.3 cm³), and the median number of metastases was 2 (range 1-32). One hundred thirty-two patients underwent whole-brain radiation therapy. Survival times were compared using recursive partitioning analysis (RPA), the Score Index for Radiosurgery (SIR), the Basic Score for Brain Metastases (BSBM), and the Diagnosis-Specific Graded Prognostic Assessment (DS-GPA). **RESULTS:** The overall survival times after SRS were compared. With the RPA index, survival times were 2.6 months (Class III, n = 27), 5.5 months (Class II, n = 348), and 13.0 months (Class I, n = 47). With the DS-GPA index, survival times were 2.8 months (Scores 0-1, n = 67), 4.2 months (Scores 1.5-2.0, n = 143), 6.6 months (Scores 2.5-3.0, n = 111), and 9.4 months (Scores 3.5-4.0, n = 101). With the SIR, survival times were 3.2 months (Scores 0-3, n = 56), 5.8 months (Scores 4-7, n = 319), and 12.7 months (Scores 8-10, n = 47). With the BSBM index, survival times were 2.6 months (BSBM0, n = 47), 5.4 months (BSBM1, n = 282), 11.0 months (BSBM2, n = 86), and 8.8 months (BSBM3, n = 7). The DS-GPA index was the most balanced by case numbers in each class and provided the overall best prognostic index for overall survival. **CONCLUSIONS:** The DS-GPA index proved most balanced and predictive of survival for patients with melanoma who underwent SRS as part of management for brain metastases. Patients whose DS-GPA score was \geq 2.5 had predictably improved survival times after SRS.

[137] Toward the complete control of brain metastases using surveillance screening and stereotactic radiosurgery.

Journal of neurosurgery. 2018;128(1):23-31

Wolf A, Kvint S, Chachoua A, Pavlick A, Wilson M, Donahue B, Golfinos JG, Silverman J, Kondziolka D

PMID: 28298015 DOI: 10.3171/2016.10.JNS161036

OBJECTIVE: The incidence of brain metastases is increasing with improved systemic therapies, many of which have a limited impact on intracranial disease. Stereotactic radiosurgery (SRS) is a first-line management option for brain metastases. The purpose of this study was to determine if there is a threshold tumor size below which local control (LC) rates approach 100%, and to relate these findings to the use of routine surveillance brain imaging. **METHODS:** From a prospective registry, 200 patients with 1237 brain metastases were identified who underwent SRS between December 2012 and May 2015. The median imaging follow-up duration was 7.9 months, and the median margin dose was 18 Gy. The maximal diameter and volume of tumors were measured. Histological analysis included 96 patients with non-small cell lung cancers (NSCLCs), 40 with melanoma, 35 with breast cancer, and 29 with other histologies. **RESULTS:** Almost 50% of brain metastases were NSCLCs and commonly measured less than 6 mm in maximal diameter or 70 mm³ in volume. Thirty-three of 1237 tumors had local progression at a median of 8.8 months. The 1- and 2-year actuarial LC rates were 97% and 93%, respectively. LC of 100% was achieved for all intracranial metastases less than 100 mm³ in volume or 6 mm in diameter. Patients whose tumors at first SRS were less than 10 mm maximal diameter or a volume of 250 mm³ had improved overall survival. **CONCLUSIONS:** SRS can achieve LC rates approaching 100% for subcentimeter metastases. The earlier initial detection and prompt treatment of small intracranial metastases may prevent the development of

neurological symptoms and the need for resection, and improve overall survival. To identify tumors when they are small, routine surveillance brain imaging should be considered as part of the standard of care for lung, breast, and melanoma metastases. CLASSIFICATION OF EVIDENCE Type of question: prognostic; study design: retrospective cohort; evidence: Class II.

[138] Local control and overall survival for adjuvant stereotactic radiosurgery in patients with residual or recurrent disease.

Journal of neuro-oncology. 2018;136(2):281-287

Nanda T, Yaeh A, Wu CC, Jani A, Saad S, Qureshi YH, Cauley KA, Lesser J, Cheng SK, Isaacson SR, Sisti MB, Bruce JN, Mckhann GM, Sheth SA, Lassman AB, Wang TJ

PMID: 29170908 DOI: 10.1007/s11060-017-2651-1

Prior studies of post-operative stereotactic radiosurgery (SRS) have not distinguished between Adjuvant SRS (ARS) versus Adjuvant SRS to residual/recurrent disease (ARD). In this study, we defined ARS and ARD and investigated local control (LC), overall survival (OS), distant development of brain metastases (DBF), and leptomeningeal disease (LMD). We retrospectively identified BM patients who received surgical resection and SRS for BM from an IRB approved database between Jan 2009-Aug 2015. Patients were stratified into two groups: ARS and ARD. LC was determined by follow-up MRI studies and OS was measured from the date of surgery. LC and OS were assessed using the Kaplan-Meier method. 70 cavities underwent surgical resection of BM and received SRS to the post-operative bed. 41 cavities were classified as ARS and 29 as ARD. There was no significant difference in 12-month LC between the ARS and ARD group (71.4 vs. 80.8%, respectively; p = 0.135) from the time point of SRS. The overall 1-year survival for ARS and ARD was 79.9 and 86.1%, respectively (p = 0.339). Mean time to progression was 6.45 and 8.0 months and median follow-up was 10 and 15 months for ARS and ARD, respectively. 11.8% of ARS patients and 15.4% of ARD patients developed LMD, p = 0.72. 29.4% of ARS and 48.0% of ARD patients developed DBF, p = 0.145. Our findings suggest that observation after surgical resection, with subsequent treatment with SRS after the development of local failure, may not compromise treatment efficacy. If validated, this would spare patients who do not recur post-surgically from additional treatment.

2017

[139] Systemic Therapy after Radiotherapy Significantly Reduces the Risk of Mortality of Patients with 1-3 Brain Metastases: A Retrospective Study of 250 Patients.

Chinese medical journal. 2017;130(24):2916-2921

Li B, Dai ZX, Chen YD, Liu YW, Liu S, Gu XN, Qiu XG

PMID: 29237923 DOI: 10.4103/0366-6999.220296

BACKGROUND: For patients with a brain metastasis (BM), systemic therapy is usually administered after the completion of radiotherapy, especially in cases of multiple BMs. However, the role of systemic therapy in patients with a limited number of BMs is not clear. Therefore, we conducted a retrospective study to explore this question. **METHODS:** Consecutive patients with a pathologically confirmed malignancy and 1-3 intracranial lesions that had been documented within the last decade were selected from the databases of three hospitals in China. **RESULTS:** A total of 250 patients were enrolled; of them, 135 received radiotherapy alone and 115 received radiotherapy plus systemic therapy. In patients receiving whole-brain radiation therapy (WBRT) as radiotherapy, 28 received WBRT alone and 35 patients received WBRT plus systemic therapy. Of the patients treated with stereotactic radiosurgery (SRS), 107 received SRS alone and 80 received SRS plus systemic therapy. Multivariate analysis revealed that systemic therapy significantly reduced the risk of mortality compared with radiotherapy alone (hazard ratio [HR] = 0.294, 95% confidence interval [CI] = 0.158-0.548). Further, when the analysis was conducted in subgroups of WBRT (HR =

0.230, 95% CI = 0.081-0.653) or SRS (HR = 0.305, 95% CI = 0.127-0.731), systemic therapy still showed the ability to reduce the risk of mortality in patients with BMs. **CONCLUSION:** Systemic therapy after either SRS or WBRT radiotherapy may significantly reduce the risk of mortality of patients with 1-3 BMs.

[140] Effect of Gamma Knife Radiosurgery and Programmed Cell Death 1 Receptor Antagonists on Metastatic Melanoma.

Cureus. 2017;9(12):e1943

Nordmann N, Hubbard M, Nordmann T, Sperduto PW, Clark HB, Hunt MA
PMID: 29468099 DOI: 10.7759/cureus.1943

LEARNING OBJECTIVES: To evaluate radiation-induced changes in patients with brain metastasis secondary to malignant melanoma who received treatment with Gamma Knife radiosurgery (GKRS) and programmed cell death 1 (PD-1) receptor antagonists. **INTRODUCTION:** Stereotactic radiosurgery and chemotherapeutics are used together for treatment of metastatic melanoma and have been linked to delayed radiation-induced vasculitic leukoencephalopathy (DRIVL). There have been reports of more intense interactions with new immunotherapeutics targeting PD-1 receptors, but their interactions have not been well described and may result in an accelerated response to GKRS. Here we present data on subjects treated with this combination from a single institution. **METHODS:** Records from patients who underwent treatment for metastatic melanoma to the brain with GKRS from 2011 to 2016 were reviewed. Demographics, date of brain metastasis diagnosis, cause of death when applicable, immunotherapeutics, and imaging findings were recorded. The timing of radiation therapy and medications were also documented. **RESULTS:** A total of 79 subjects were treated with GKRS, and 66 underwent treatment with both GKRS and immunotherapy. Regarding the 30 patients treated with anti-PD-1 immunotherapy, 21 patients received pembrolizumab, seven patients received nivolumab, and two patients received pembrolizumab and nivolumab. Serial imaging was available for interpretation in 25 patients, with 13 subjects who received GKRS and anti-PD-1 immunotherapy less than six weeks of each other. While four subjects had indeterminate/mixed findings on subsequent magnetic resonance imaging (MRI), nine subjects were noted to have progression. Two of these patients showed progression but subsequent imaging revealed a decrease in progression or improvement on MRI to previously targeted lesions by GKRS. None of the 13 subjects had surgery following their combined therapies. **CONCLUSIONS:** This data suggests that there is need for further investigation of the role for concurrent treatment with PD-1 inhibitors and GKRS to enhance the treatment of metastatic melanoma. We present data on 13 patients who appear to have some radiologic benefit to this treatment combination, two of whom had radiographic pseudoprogression.

[141] Optimization of diagnostic performance for differentiation of recurrence from radiation necrosis in patients with metastatic brain tumors using tumor volume-corrected (11)C-methionine uptake.

EJNMMI research. 2017;7(1):45

Jung TY, Kim IY, Lim SH, Park KS, Kim DY, Jung S, Moon KS, Jang WY, Kang SR, Cho SG, Min JJ, Bom HS, Kwon SY

PMID: 28536967 DOI: 10.1186/s13550-017-0293-0

BACKGROUND: Tumor to normal tissue ratio (T/N ratio) on (11)C-methionine ((11)C-MET) positron emission tomography/computed tomography (PET/CT) is affected by variable factors. We investigated whether T/N ratio cutoff values corrected according to metabolic tumor volume (MTV) could improve the diagnostic performance of (11)C-MET PET/CT for diagnosis of recurrence in patients with metastatic brain tumor. Forty-eight patients with metastatic brain tumors underwent (11)C-MET PET/CT for differential diagnosis between recurrence and radiation necrosis after gamma knife radiosurgery (GKR). Both T/N ratio and MTV were estimated in each lesion on (11)C-MET PET/CT. The lesions were classified into three groups based on MTV criteria (≤ 0.5 cm³); > 0.5 , ≤ 4.0 cm³); and > 4.0 cm³). The optimal cutoff values of the T/N ratio from receiver operating characteristic (ROC) curve were determined in each group (MTV-corrected) as well as total lesions (non-corrected). Finally, diagnostic

performance of (11)C-MET PET/CT was compared with the MTV-corrected cutoff values. **RESULTS:** Among 77 lesions, 51 were diagnosed with recurrence. The mean T/N ratio was 2.25 (+/- 1.12) for recurrent lesions and 1.44 (+/- 0.22) for radiation necrosis (P < 0.001). T/N ratio of 1.61 (non-corrected) provided the best sensitivity, specificity, and diagnostic accuracy (70.6, 80.8, and 74.0%, respectively). Using the MTV criteria, optimal cutoff values of the T/N ratios in each group were 1.23 (MTV ≤ 0.5 cm³), 1.54 (0.5 cm³ < MTV ≤ 4.0 cm³), and 1.85 (MTV > 4.0 cm³). In small-sized lesions (MTV ≤ 0.5 cm³), MTV-corrected cutoff values (1.23) could maintain favorable diagnostic performance with sensitivity, specificity, and diagnostic accuracy (70.0, 80.0, and 73.3%, respectively), compared to non-corrected cutoff values. **CONCLUSIONS:** MTV-corrected cutoff values of T/N ratio could maintain the diagnostic performance of (11)C-MET PET/CT in small sized, metastatic brain tumors. We expect our results to contribute to reproducible and standardized interpretation of (11)C-MET PET/CT.

[142] Prognostic Factors for Survival of Patients With Synchronous or Metachronous Brain Metastasis of Renal Cell Carcinoma.

Clinical genitourinary cancer. 2017;15(6):717-723

Choi SY, Yoo S, You D, Jeong IG, Song C, Hong B, Hong JH, Ahn H, Kim CS
PMID: 28552571 DOI: 10.1016/j.clgc.2017.05.010

INTRODUCTION: We evaluated the oncological outcomes of synchronous or metachronous brain metastasis (BM) of metastatic renal cell carcinoma (RCC) according to clinicopathologic factors. **PATIENTS AND METHODS:** Patients with metastatic RCC (n = 93) with synchronous and metachronous BM were retrospectively identified. We analyzed patients and tumor characteristics, treatment methods, prognostic factors, BM progression, and overall survival (OS). **RESULTS:** Seventy-six patients (81.7%) received local therapy (stereotactic radiosurgery [60.2%], radiation therapy [22.6%], and neurosurgery [10.8%]), and 54 patients (58.1%) were treated with systemic medical therapy. In multivariable analysis, poor Memorial Sloan-Kettering Cancer Center (MSKCC) risk (hazard ratio [HR] 3.672; 95% confidence interval [CI], 1.441-9.36; P = .0064), sarcomatoid component (HR 4.264; 95% CI, 2.062-8.820; P = .0001), and multiple BMs (HR 2.838; 95% CI, 1.690-4.767; P = .0001) were prognostic indicators of a poorer OS outcome. Local (HR 0.436; 95% CI, 0.237-0.802; P = .0076) and systemic treatment (HR 0.322; 95% CI, 0.190-0.548; P < .0001) were independent factors for a better OS. Although OS from initial RCC diagnosis in patients with metachronous BM was better than that for patients with synchronous BM, there were no differences found between synchronous and metachronous patients in terms of BM progression and OS after the diagnosis of BM. **CONCLUSIONS:** Poor MSKCC risk, sarcomatoid component of histology, and multiple BMs are prognostic indicators for poor OS in patients with BM from metastatic RCC. Systemic and/or local treatment improves the OS. Because the type of BM, synchronous or metachronous, does not influence BM progression or the OS outcome, routine evaluation for BM is not recommended.

[143] Stereotactic Radiosurgery With or Without Whole-Brain Radiation Therapy for Limited Brain Metastases: A Secondary Analysis of the North Central Cancer Treatment Group N0574 (Alliance) Randomized Controlled Trial.

International journal of radiation oncology, biology, physics. 2017;99(5):1173-1178

Churilla TM, Ballman KV, Brown PD, Twohy EL, Jaeckle K, Farace E, Cerhan JH, Anderson SK, Carrero XW, Garces YI, Barker FG 2nd, Deming R, Dixon JG, Burri SH, Chung C, Menard C, Stieber VW, Pollock BE, Galanis E, Buckner JC, Asher AL
PMID: 28939223 DOI: 10.1016/j.ijrobp.2017.07.045

PURPOSE: To determine whether whole-brain radiation therapy (WBRT) is associated with improved overall survival among non-small cell lung cancer (NSCLC) patients with favorable prognoses at diagnosis. **METHODS AND MATERIALS:** In the N0574 trial, patients with 1 to 3 brain metastases were randomized to receive stereotactic radiosurgery (SRS) or SRS plus WBRT (SRS + WBRT), with a primary endpoint of cognitive deterioration. We calculated diagnosis-specific graded prognostic assessment (DS-GPA) scores for NSCLC patients and evaluated overall survival according to receipt of WBRT and DS-GPA

score using 2 separate cut-points (≥ 2.0 vs < 2.0 and ≥ 2.5 vs < 2.5). **RESULTS:** A total of 126 NSCLC patients were included for analysis, with median follow-up of 14.2 months. Data for DS-GPA calculation were available for 86.3% of all enrolled NSCLC patients. Overall, 50.0% of patients had DS-GPA score ≥ 2.0 , and 23.0% of patients had DS-GPA scores ≥ 2.5 . The SRS and SRS + WBRT groups were well balanced with regard to prognostic factors. The median survival according to receipt of WBRT was 11.3 months (+WBRT) and 17.9 months (-WBRT) for patients with DS-GPA ≥ 2.0 (favorable prognoses, $P = .63$; hazard ratio 0.86; 95% confidence interval 0.47-1.59). Median survival was 3.7 months (+WBRT) and 6.6 months (-WBRT) for patients with DS-GPA < 2.0 patients (unfavorable prognoses, $P = .85$; hazard ratio 0.95; 95% confidence interval 0.56-1.62). Outcomes according to the receipt of WBRT and DS-GPA remained similar utilizing DS-GPA ≥ 2.5 as a cutoff for favorable prognoses. There was no interaction between the continuum of the DS-GPA groups and WBRT on overall survival ($P = .53$). **CONCLUSIONS:** We observed no significant differences in survival according to receipt of WBRT in favorable-prognosis NSCLC patients. This study further supports the approach of SRS alone in the majority of patients with limited brain metastases.

[144] Survival Patterns of 5750 Stereotactic Radiosurgery-Treated Patients with Brain Metastasis as a Function of the Number of Lesions.

World neurosurgery. 2017;107:944-951.e1

Ali MA, Hirshman BR, Wilson B, Carroll KT, Proudfoot JA, Goetsch SJ, Alksne JF, Ott K, Aiyama H, Nagano O, Carter BS, Fogarty G, Hong A, Serizawa T, Yamamoto M, Chen CC

PMID: 28735121 DOI: 10.1016/j.wneu.2017.07.062

BACKGROUND: The number of brain metastases (BMs) plays an important role in the decision between stereotactic radiosurgery (SRS) and whole-brain radiation therapy. **METHODS:** We analyzed the survival of 5750 SRS-treated patients with BM as a function of BM number. Survival analyses were performed with Kaplan-Meier analysis as well as univariate and multivariate Cox proportional hazards models. **RESULTS:** Patients with BMs were first categorized as those with 1, 2-4, and 5-10 BMs based on the scheme proposed by Yamamoto et al. (*Lancet Oncology* 2014). Median overall survival for patients with 1 BM was superior to those with 2-4 BMs (7.1 months vs. 6.4 months, $P = 0.009$), and survival of patients with 2-4 BMs did not differ from those with 5-10 BMs (6.4 months vs. 6.3 months, $P = 0.170$). The median survival of patients with > 10 BMs was lower than those with 2-10 BMs (6.3 months vs. 5.5 months, $P = 0.025$). In a multivariate model that accounted for age, Karnofsky Performance Score, systemic disease status, tumor histology, and cumulative intracranial tumor volume, we observed an approximately 10% increase in hazard of death when comparing patients with 1 versus 2-10 BMs ($P < 0.001$) or 10 versus > 10 BMs ($P < 0.001$). When BM number was modeled as a continuous variable rather than using the classification by Yamamoto et al., we observed a step-wise 4% increase in the hazard of death for every increment of 6-7 BM ($P < 0.001$). **CONCLUSIONS:** The contribution of BM number to overall survival is modest and should be considered as one of the many variables considered in the decision between SRS and whole-brain radiation therapy.

[145] The effect of timing of stereotactic radiosurgery treatment of melanoma brain metastases treated with ipilimumab.

Journal of neurosurgery. 2017;127(5):1007-1014

Cohen-Inbar O, Shih HH, Xu Z, Schlesinger D, Sheehan JP

PMID: 28059663 DOI: 10.3171/2016.9.JNS161585

OBJECTIVE: Melanoma represents the third most common cause of CNS metastases. Immunotherapy has evolved as a treatment option for patients with Stage IV melanoma. Stereotactic radiosurgery (SRS) also elicits an immune response within the brain and may interact with immunotherapy. The authors report on a cohort of patients treated for brain metastases with immunotherapy and evaluate the effect of SRS timing on the intracranial response. **METHODS:** All consecutively treated melanoma patients receiving ipilimumab and SRS for treatment of brain metastases at the University of Virginia between 2009 and 2014 were included in this retrospective analysis; data from 46 patients harboring

232 brain metastases were reviewed. The median duration of clinical follow-up was 7.9 months (range 3-42.6 months). The median age of the patients was 63 years (range 24.3-83.6 years). Thirty-two patients received SRS before or during ipilimumab cycles (Group A), whereas 14 patients received SRS after ipilimumab treatment (Group B). Radiographic and clinical responses were assessed at approximately 3-month intervals after SRS. **RESULTS:** The 2 cohorts were comparable in pertinent baseline characteristics with the exception of SRS timing relative to ipilimumab. Local recurrence-free duration (LRFD) was significantly longer in Group A (median 19.6 months, range 1.1-34.7 months) than in Group B patients (median 3 months, range 0.4-20.4 months) ($p = 0.002$). Post-SRS perilesional edema was more significant in Group A. **CONCLUSIONS:** The effect of SRS and ipilimumab on LRFD seems greater when SRS is performed before or during ipilimumab treatments. The timing of immunotherapy and SRS may affect LRFD and postradiosurgical edema. The interactions between immunotherapy and SRS warrant further investigation so as to optimize the therapeutic benefits and mitigate the risks associated with multimodality, targeted therapy.

[146] Robustness of the neurological prognostic score in brain metastasis patients treated with Gamma Knife radiosurgery.

Journal of neurosurgery. 2017;127(5):1000-1006

Serizawa T, Higuchi Y, Nagano O, Matsuda S, Aoyagi K, Ono J, Saeki N, Iwadate Y, Hirai T, Takemoto S, Shibamoto Y

PMID: 27911235 DOI: 10.3171/2016.8.JNS16528

OBJECTIVE: The neurological prognostic score (NPS) was recently proposed as a means for predicting neurological outcomes, such as the preservation of neurological function and the prevention of neurological death, in brain metastasis patients treated with Gamma Knife radiosurgery (GKRS). NPS consists of 2 groups: Group A patients were expected to have better neurological outcomes, and Group B patients were expected to have poorer outcomes. NPS robustness was tested in various situations. **METHODS:** In total, 3040 patients with brain metastases that were treated with GKRS were analyzed. The cumulative incidence of the loss of neurological function independence (i.e., neurological deterioration) was estimated using competing risk analysis, and NPS was compared between Groups A and B by employing Gray's model. NPS was tested to determine if it can be applied to 5 cancer categories-non-small cell lung cancer, small cell lung cancer, gastrointestinal tract cancer, breast cancer, and other cancers-as well as if it can be incorporated into the 5 major grading systems: recursive partitioning analysis (RPA), score index for stereotactic radiosurgery (SIR), basic score for brain metastases (BSBM), graded prognostic assessment (GPA), and modified-RPA (M-RPA). **RESULTS:** There were 2263 patients in NPS Group A and 777 patients in Group B. Neurological deterioration was observed in 586 patients (19.2%). The cumulative incidences of neurological deterioration were 9.5% versus 21.0%, 14.1% versus 25.4%, and 17.6% versus 27.8% in NPS Groups A and B at 1, 2, and 5 years, respectively. Significant differences were detected between the NPS groups in all cancer categories. There were significant differences between NPS Groups A and B for all classes in terms of the BSBM, GPA, and M-RPA systems, but the differences failed to reach statistical significance in terms of RPA Class I and SIR Class 0 to 3. **CONCLUSIONS:** The NPS was verified as being highly applicable to all cancer categories and almost all classes for the 5 grading systems in terms of neurological function independence. This NPS system appears to be quite robust in various situations for brain metastasis patients treated with GKRS.

[147] Resection and Observation for Brain Metastasis without Prompt Postoperative Radiation Therapy.

Journal of Korean Neurosurgical Society. 2017;60(6):667-675

Song TW, Kim IY, Jung S, Jung TY, Moon KS, Jang WY

PMID: 29142626 DOI: 10.3340/jkns.2017.0404.002

OBJECTIVE: Total resection without consecutive postoperative whole brain radiation therapy is indicated for patients with a single or two sites of brain metastasis, with close follow-up by serial magnetic resonance imaging (MRI). In

this study, we explored the effectiveness, usefulness, and safety of this follow-up regimen. **METHODS:** From January 2006 to December 2015, a total of 109 patients (76 males, 33 females) underwent tumor resection as the first treatment for brain metastases (97 patients with single metastases, 12 with two metastases). The mean age was 59.8 years (range 27-80). The location of the 121 tumors in the 109 patients was supratentorial (n=98) and in the cerebellum (n=23). The origin of the primary cancers was lung (n=45), breast (n=17), gastrointestinal tract (n=18), hepatobiliary system (n=8), kidney (n=7), others (n=11), and unknown origin (n=3). The 121 tumors were totally resected. Follow-up involved regular clinical and MRI assessments. Recurrence-free survival (RFS) and overall survival (OS) after tumor resection were analyzed by Kaplan-Meier methods based on clinical prognostic factors. **RESULTS:** During the follow-up, MRI scans were done for 85 patients (78%) with 97 tumors. Fifty-six of the 97 tumors showed no recurrence without adjuvant local treatment, representing a numerical tumor recurrence-free rate of 57.7%. Mean and median RFS was 13.6 and 5.3 months, respectively. Kaplan-Meier analysis revealed the cerebellar location of the tumor as the only statistically significant prognostic factor related to RFS ($p=0.020$). Mean and median OS was 15.2 and 8.1 months, respectively. There were no significant prognostic factors related to OS. The survival rate at one year was 8.2% (9 of 109). **CONCLUSION:** With close and regular clinical and image follow-up, initial postoperative observation without prompt postoperative radiation therapy can be applied in patients of brain metastasi(e)s when both the tumor(s) are completely resected.

[148] Distant intracranial failure in melanoma brain metastases treated with stereotactic radiosurgery in the era of immunotherapy and targeted agents.

Advances in radiation oncology. 2017;2(4):572-580

Acharya S, Mahmood M, Mullen D, Yang D, Tsien CI, Huang J, Perkins SM, Rich K, Chicoine M, Leuthardt E, Dowling J, Dunn G, Keller J, Robinson CG, Abraham C PMID: 29204524 DOI: 10.1016/j.adro.2017.07.003

PURPOSE: Stereotactic radiosurgery (SRS) in combination with immunotherapy (IMT) or targeted therapy is increasingly being used in the setting of melanoma brain metastases (MBMs). The synergistic properties of combination therapy are not well understood. We compared the distant intracranial failure rates of intact MBMs treated with SRS, SRS + IMT, and SRS + targeted therapy. **METHODS AND MATERIALS:** Combination therapy was defined as delivery of SRS within 3 months of IMT (anti-CTLA-4 /anti-PD-1 therapy) or targeted therapy (BRAF/MEK inhibitors). The primary endpoint was distant intracranial failure after SRS, which was defined as any new MBM identified on brain magnetic resonance imaging. Outcomes were evaluated using the Kaplan Meier method and Cox proportional hazards. **RESULTS:** A total of 72 patients with melanoma with 233 MBMs were treated between April 2006 and April 2016. The number of MBMs within each treatment group was as follows: SRS: 121; SRS + IMT: 48; and SRS + targeted therapy: 64. The median follow-up was 8.9 months. One-year distant intracranial control rates for SRS, SRS + IMT, and SRS + targeted therapy were 11.5%, 60%, and 10%, respectively ($P < .001$). On multivariate analysis, after adjusting for steroid use and number of MBMs, SRS + IMT remained associated with a significant reduction in distant intracranial failure compared with SRS (hazard ratio [HR], 0.48; 95% confidence interval [CI], 0.29-0.80; $P = .003$) and compared with SRS + targeted therapy (HR, 0.41; 95% CI, 0.25-0.68; $P = .001$). One-year local control for SRS, SRS + IMT, and SRS + targeted therapy was 66%, 85%, and 72%, respectively ($P = .044$). On multivariate analysis, after adjusting for dose, SRS + IMT remained associated with a significant reduction in local failure compared with SRS alone (HR, 0.37; 95% CI, 0.14-0.95; $P = .04$). **CONCLUSIONS:** SRS with immunotherapy is associated with decreased distant and local intracranial failure compared with SRS alone. Prospective studies are warranted to validate this result.

[149] Stereotactic radiosurgery of early melanoma brain metastases after initiation of anti-CTLA-4 treatment is associated with improved intracranial control.

Radiation therapy and oncology : journal of the European Society for Therapeutic

Radiology and Oncology. 2017;125(1):80-88

An Y, Jiang W, Kim BYS, Qian JM, Tang C, Fang P, Logan J, D'Souza NM, Haydu LE, Wang XA, Hess KR, Kluger H, Glitza IC, Mahajan A, Welsh JW, Lin SH, Yu JB, Davies MA, Hwu P, Sulman EP, Brown PD, Chiang VLS, Li J PMID: 28916225 DOI: 10.1016/j.radonc.2017.08.009

BACKGROUND: Numerous studies suggest that radiation can boost antitumor immune response by stimulating release of tumor-specific antigens. However, the optimal timing between radiotherapy and immune checkpoint blockade to achieve potentially synergistic benefits is unclear. **MATERIAL AND METHODS:** Multi-institutional retrospective analysis was conducted of ninety-nine metastatic melanoma patients from 2007 to 2014 treated with ipilimumab who later received stereotactic radiosurgery (SRS) for new brain metastases that developed after starting immunotherapy. All patients had complete blood count acquired before SRS. Primary outcomes were intracranial disease control and overall survival (OS). **RESULTS:** The median follow-up time was 15.5 months. In the MD Anderson cohort, patients who received SRS after 5.5 months (n=20) of their last dose of ipilimumab had significantly worse intracranial control than patients who received SRS within 5.5 months (n=51) (median 3.63 vs. 8.09 months; hazard ratio [HR] 2.07, 95% confidence interval [CI] 1.03-4.16, $p=0.041$). OS was not different between the two arms. The improvement in intracranial control was confirmed in an independent validation cohort of 28 patients treated at Yale-New Haven Hospital. Circulating absolute lymphocyte count before SRS predicted for treatment response as those with baseline counts $>1000/\text{microL}$ had reduced risk of intracranial recurrence compared with those with $\leq 1000/\text{microL}$ (HR 0.46, 95% CI 0.023-0.94, $p=0.03$). **CONCLUSIONS:** In this multi-institutional study, patients who received SRS for new brain metastases within 5.5 months after ipilimumab therapy had better intracranial disease control than those who received SRS later. Moreover, higher circulating lymphocyte count was associated with improved intracranial disease control.

[150] Survival of melanoma patients treated with targeted therapy and immunotherapy after systematic upfront control of brain metastases by radiosurgery.

European journal of cancer (Oxford, England : 1990). 2017;84:44-54

Gaudy-Marqueste C, Dussouil AS, Carron R, Troin L, Malissen N, Loundou A, Monestier S, Mallet S, Richard MA, Regis JM, Grob JJ PMID: 28783540 DOI: 10.1016/j.ejca.2017.07.017

BACKGROUND: Targeted therapy (TT) and immunotherapies (ITs) have dramatically improved survival in metastatic melanoma (MM). However, their efficacy on brain metastasis (BM) remains limited and poorly documented. **PATIENTS AND METHODS:** Retrospective cohort of consecutive MM patients (pts) with BMs, all systematically upfront treated by Gamma-Knife (GK) at first BM and retreated in case of new BMs, from 2010 to 2015 at the time when ipilimumab BRAF +/- MEK inhibitors and anti-PD1 were introduced in practice. Survival after 1st GK (OSGK1) according to prognostic factors and treatment. **RESULTS:** Among 179 consecutive pts treated by GK, 109 received IT and/or TT after the 1st GK. Median OSGK1 was 10.95 months and 1- and 2-year survival rates were 49.5% and 27.4%, respectively, versus a median overall survival (OS) of 2.29 months ($p < .001$) in those who did not receive IT or TT. In pts who initially had a single BM, median OS and 1- and 2-year survival rates were 14.46 months, 66.7% and 43.4%, respectively; in pts with 2-3 BMs: 8.85 months, 46.4% and 31%, respectively; in pts with >3 BMs: 7.25 months, 37.2% and 11.9%, respectively. Multivariate analysis for OSGK1 confirmed that IT and TT were significantly and highly protective. Best OSGK1 was observed in BRAF-wild-type pts receiving anti-PD1 or in BRAF-mutated pts receiving BRAF-inhibitors and anti-PD1 (12.26 and 14.82 months, respectively). **CONCLUSION:** In real-life MM pts with BMs, a strategy aiming at controlling BM with GK together with TT and/or IT seems to achieve unprecedented survival rates.

[151] Whole brain radiotherapy after stereotactic radiosurgery or surgical resection among patients with one to three brain metastases and favorable prognoses: a secondary analysis of EORTC 22952-26001.

Annals of oncology : official journal of the European Society for Medical Oncology. 2017;28(10):2588-2594

Churilla TM, Handorf E, Collette S, Collette L, Dong Y, Aizer AA, Kocher M, Soffietti R, Alexander BM, Weiss SE
PMID: 28961826 DOI: 10.1093/annonc/mdx332

BACKGROUND: The absence of a survival benefit for whole brain radiotherapy (WBRT) among randomized trials has been attributed to a competing risk of death from extracranial disease. We re-analyzed EORTC 22952 to assess the impact of WBRT on survival for patients with controlled extracranial disease or favorable prognoses. **PATIENTS AND METHODS:** We utilized Cox regression, landmark analysis, and the Kaplan-Meier method to evaluate the impact of WBRT on survival accounting for (i) extracranial progression as a time-dependent covariate in all patients and (ii) diagnosis-specific graded prognostic assessment (GPA) score in patients with primary non-small-cell lung cancer (NSCLC). **RESULTS:** A total of 329 patients treated per-protocol were included for analysis with a median follow up of 26 months. One hundred and fifteen (35%) patients had no extracranial progression; 70 (21%) patients had progression <90 days, 65 (20%) between 90 and 180 days, and 79 (24%) patients >180 days from randomization. There was no difference in the model-based risk of death in the WBRT group before [hazard ratio (HR) (95% CI)=0.70 (0.45-1.11), P = 0.133], or after [HR (95% CI)=1.20 (0.89-1.61), P = 0.214] extracranial progression. Among 177 patients with NSCLC, 175 had data available for GPA calculation. There was no significant survival benefit to WBRT among NSCLC patients with favorable GPA scores [HR (95% CI)=1.10 (0.68-1.79)] or unfavorable GPA scores [HR (95% CI)=1.11 (0.71-1.76)]. **CONCLUSIONS:** Among patients with limited extracranial disease and one to three brain metastases at enrollment, we found no significant survival benefit to WBRT among NSCLC patients with favorable GPA scores or patients with any histology and controlled extracranial disease status. This exploratory analysis of phase III data supports the practice of omitting WBRT for patients with limited brain metastases undergoing SRS and close surveillance. Clinical Trials Number: NCT00002899.

[152] Cumulative Intracranial Tumor Volume and Number of Brain Metastasis as Predictors of Developing New Lesions After Stereotactic Radiosurgery for Brain Metastasis.

World neurosurgery. 2017;106:666-675

Sharma M, Jia X, Ahluwalia M, Barnett GH, Vogelbaum MA, Chao ST, Suh JH, Murphy ES, Yu JS, Angelov L, Mohammadi AM
PMID: 28735139 DOI: 10.1016/j.wneu.2017.07.048

OBJECTIVES: To identify risk factors associated with early distant radiographic progression in patients undergoing stereotactic radiosurgery (SRS) for brain metastases (BM). **METHODS:** Following Institutional Review Board approval, data of 1427 patients (4283 BM lesions) who were treated by SRS at the Cleveland Clinic for 2000-2012 were collected. Local tumor progression (LTP), distant tumor progression (DTP), and radiographic radiation necrosis (RN) were the primary endpoints. Patient, imaging, radiosurgery, and tumor variables and follow-up data were collected. **RESULTS:** The median number of targets was 2 (range, 1-17); 45% of the patients had a single lesion. DTP was observed in 10% at 3 months and 19% at 6 months. Patients with 5-10 target lesions for SRS were more likely to develop new lesions at both 3 and 6 months compared to those with 2-4 lesions (odds ratio [OR], 0.83, 95% confidence interval [CI], 0.40-0.85 and OR, 0.85, 95% CI, 0.45-0.86 respectively; P < 0.05). Younger age (<65 years; P < 0.001), higher number of lesions (>1; P < 0.001), cumulative intracranial tumor volume (CITV) <2.75 cc (P = 0.023), type of SRS (upfront and salvage vs. boost; P < 0.001), and tumor pathology (radiosensitive; P < 0.001), were independent predictors of early distant tumor progression following SRS. **CONCLUSIONS:** The number of target lesions and low CITV are both independent predictors of early DTP following SRS for BM. Radiosensitive tumor histology, younger age (<65 years), and SRS without

previous whole-brain radiation therapy (upfront or salvage) were also predictors of early DTP.

[153] First follow-up radiographic response is one of the predictors of local tumor progression and radiation necrosis after stereotactic radiosurgery for brain metastases.

Cancer medicine. 2017;6(9):2076-2086

Sharma M, Jia X, Ahluwalia M, Barnett GH, Vogelbaum MA, Chao ST, Suh JH, Murphy ES, Yu JS, Angelov L, Mohammadi AM
PMID: 28776956 DOI: 10.1002/cam4.1149

Local progression (LP) and radiation necrosis (RN) occur in >20% of cases following stereotactic radiosurgery (SRS) for brain metastases (BM). Expected outcomes following SRS for BM include tumor control/shrinkage, local progression and radiation necrosis. 1427 patients with 4283 BM lesions were treated using SRS at Cleveland Clinic from 2000 to 2012. Clinical, imaging and radiosurgery data were collected from the database. Local tumor progression and RN were the primary end points and correlated with patient and tumor-related variables. 5.7% of lesions developed radiographic RN and 3.6% showed local progression at 6 months. Absence of new extracranial metastasis (P < 0.001), response to SRS at first follow-up scan (local progression versus stable size (P < 0.001), partial resolution versus complete resolution at first follow up [P = 0.009]), prior SRS to the same lesion (P < 0.001), IDL% (</=55; P < 0.001), maximum tumor diameter (>0.9 cm; P < 0.001) and MD/PD gradient index (</=1.8, P < 0.001) were independent predictors of high risk of local tumor progression. Absence of systemic metastases (P = 0.029), good neurological function at 1st follow-up (P </= 0.001), no prior SRS to other lesion (P = 0.024), low conformity index (</=1.9) (P = 0.009), large maximum target diameter (>0.9 cm) (P = 0.003) and response to SRS (tumor progression vs. stable size following SRS [P < 0.001]) were independent predictors of high risk of radiographic RN. Complete tumor response at first follow-up, maximum tumor diameter <0.9 cm, tumor volume <2.4 cc and no prior SRS to the index lesion are good prognostic factors with reduced risk of LP following SRS. Complete tumor response to SRS, poor neurological function at first follow-up, prior SRS to other lesions and high conformity index are favorable factors for not developing RN. Stable or partial response at first follow-up after SRS have same impact on local progression and RN compared to those with complete resolution or progression.

[154] Leptomeningeal failure in patients with breast cancer receiving stereotactic radiosurgery for brain metastases.

Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2017;43:6-10

Wang EC, Huang AJ, Huang KE, McTyre ER, Lo HW, Watabe K, Metheny-Barlow L, Laxton AW, Tatter SB, Strowd RE, Chan MD, Page BR
PMID: 28511975 DOI: 10.1016/j.jocn.2017.04.033

PURPOSE: Prior studies suggest a high incidence of leptomeningeal failure (LMF) in breast cancer metastatic to brain. This study examines breast cancer-specific variables affecting development of LMF and survival after Gamma-Knife Radiosurgery (GKS). **METHODS:** Between 2000-2010, 149 (breast) and 658 other-histology patients were treated with GKS. Hormone/HER2, age, local/distant brain failure, prior craniotomy, and prior whole-brain radiotherapy (WBRT) were assessed. Median follow-up was 54months (range, 0-106). Serial MRI determined local and distant-brain failure and LMF. Statistical analysis with categorical/continuous data comparisons were done with Fisher's-exact, Wilcoxon rank-sum, log-rank tests, and Cox-Proportional Hazard models. **RESULTS:** Of 149 patients, 21 (14%) developed LMF (median time of 11.9months). None of the following predicted for LMF: Her2-status (HR=0.49, p=0.16), hormone-receptor status (HR=1.15, p=0.79), prior craniotomy (HR=1.58, p=0.42), prior WBRT (HR=1.36, p=0.55). Non-significant factors between patients that did (n=21) and did not (n=106) develop LMF included neurologic death (p=0.34) and median survival (8.6 vs 14.2months, respectively). Breast patients who had distant-failure after GKS (65/149; 43.6%) were more likely to later develop LMF (HR 4.2, p=0.005); including 15/65 (23%) patients who had distant-failure and developed LMF. Median time-

to-death for patients experiencing LMF was 6.1 months (IQR 3.4-7.8) from onset of LMF. Median survival from LMF to death was much longer in breast (6.1 months) than in other (1.7 months) histologies. **CONCLUSION:** Breast cancer patients had a longer survival after diagnosis of LMF versus other histologies. Neither ER/PR/HER2 status, nor prior surgery or prior WBRT predicted for development of LMF in breast patients.

[155] A Multi-institutional Prospective Observational Study of Stereotactic Radiosurgery for Patients With Multiple Brain Metastases (JLGK0901 Study Update): Irradiation-related Complications and Long-term Maintenance of Mini-Mental State Examination Scores.

International journal of radiation oncology, biology, physics. 2017;99(1):31-40
Yamamoto M, Serizawa T, Higuchi Y, Sato Y, Kawagishi J, Yamanaka K, Shuto T, Akabane A, Jokura H, Yomo S, Nagano O, Aoyama H
PMID: 28816158 DOI: 10.1016/j.ijrobp.2017.04.037

PURPOSE: The JLGK0901 study showed the noninferiority of stereotactic radiosurgery (SRS) alone as initial treatment of 5 to 10 brain metastases (BMs) compared with 2 to 4 BMs in terms of overall survival and most secondary endpoints (Lancet Oncol 2014;15:387-95). However, observation periods were not long enough to allow confirmation of the long-term safety of SRS alone in patients with 5 to 10 BMs. **METHODS AND MATERIALS:** This was a prospective observational study of Gamma Knife SRS-treated patients with 1 to 10 newly diagnosed BMs enrolled at 23 facilities between March 1, 2009, and February 15, 2012. **RESULTS:** The 1194 eligible patients were categorized into the following groups: group A, 1 tumor (n=455); group B, 2 to 4 tumors (n=531); and group C, 5 to 10 tumors (n=208). Cumulative rates of Mini-Mental State Examination (MMSE) score maintenance (MMSE score decrease <3 from baseline) determined with a competing risk analysis of groups A, B, and C were 93%, 91%, and 92%, respectively, at the 12th month after SRS; 91%, 89%, and 91%, respectively, at the 24th month; 89%, 88%, and 89%, respectively, at the 36th month; and 87%, 86%, and 89%, respectively, at the 48th month (hazard ratio [HR] of group A vs group B, 0.719; 95% confidence interval [CI], 0.437-1.172; P=.18; HR of group B vs group C, 1.280; 95% CI, 0.696-2.508; P=.43). During observations ranging from 0.3 to 67.5 months (median, 12.0 months; interquartile range, 5.8-26.5 months), as of December 2014, 145 patients (12.1%) had SRS-induced complications. Cumulative complication incidences by competing risk analysis for groups A, B, and C were 7%, 8%, and 6%, respectively, at the 12th month after SRS; 10%, 11%, and 11%, respectively, at the 24th month; 11%, 11%, and 12%, respectively, at the 36th month; and 12%, 12%, and 13%, respectively, at the 48th month (HR of group A vs group B, 0.850; 95% CI, 0.592-1.220; P=.38; HR of group B vs group C, 1.052; 95% CI, 0.666-1.662, P=.83). Leukoencephalopathy occurred in 12 of the 1074 patients (1.1%) with follow-up magnetic resonance imaging and was detected after salvage whole-brain radiation therapy in 11 of these 12 patients. In these 11 patients, leukoencephalopathy was detected by magnetic resonance imaging 5.2 to 21.2 months (median, 11.0 months; interquartile range, 7.0-14.4 months) after whole-brain radiation therapy. **CONCLUSIONS:** Neither MMSE score maintenance nor post-SRS complication incidence differed among groups A, B, and C. This longer-term follow-up study further supports the already-reported noninferiority hypothesis of SRS alone for patients with 5 to 10 BMs versus 2 to 4 BMs.

[156] Stereotactic radiosurgery for small brain metastases and implications regarding management with systemic therapy alone.

Journal of neuro-oncology. 2017;134(2):289-296
Trifiletti DM, Hill C, Cohen-Inbar O, Xu Z, Sheehan JP
PMID: 28577030 DOI: 10.1007/s11060-017-2519-4

While stereotactic radiosurgery (SRS) has been shown effective in the management of brain metastases, small brain metastases (<=10 mm) can pose unique challenges. Our aim was to investigate the efficacy of SRS in the treatment of small brain metastases, as well as elucidate clinically relevant factors impacting local failure (LF). We utilized a large, single-institution cohort to perform a retrospective analysis of patients with brain metastases up to 1 cm in maximal dimension. Clinical and

radiosurgical parameters were investigated for an association with LF and compared using a competing risk model to calculate cumulative incidence functions, with death and whole brain radiotherapy serving as competing risks. 1596 small brain metastases treated with SRS among 424 patients were included. Among these tumors, 33 developed LF during the follow-up period (2.4% at 12 months following SRS). Competing risk analysis demonstrated that LF was dependent on tumor size (0.7% if <=2 mm and 3.0% if 2-10 mm at 12 months, p = 0.016). Other factors associated with increasing risk of LF were the decreasing margin dose, increasing maximal tumor diameter, volume, and radioresistant tumors (each p < 0.01). 22 tumors (0.78%) developed radiographic radiation necrosis following SRS, and this incidence did not differ by tumor size (<=2 mm and 2-10 mm, p = 0.200). This large analysis confirms that SRS remains an effective modality in treatment of small brain metastases. In light of the excellent local control and relatively low risk of toxicity, patients with small brain metastases who otherwise have a reasonable expected survival should be considered for radiosurgical management.

[157] The Prognostic Role of Tumor Volume in the Outcome of Patients with Single Brain Metastasis After Stereotactic Radiosurgery.

World neurosurgery. 2017;104:229-238
Bennett EE, Angelov L, Vogelbaum MA, Barnett GH, Chao ST, Murphy ES, Yu JS, Suh JH, Jia X, Stevens GHJ, Ahluwalia MS, Mohammadi AM
PMID: 28478250 DOI: 10.1016/j.wneu.2017.04.156

BACKGROUND: Patients with single brain metastasis (SBM) have better outcomes after stereotactic radiosurgery (SRS). We analyzed our SRS database to evaluate possible prognostic factors in patients with SBM. **METHODS:** A total of 584 patients with SBM were treated with SRS at our institution (2000-2012). Study end points were overall survival (OS), and distant and local intracranial progression-free survival (DPFS and LPFS, respectively). Multivariable analysis was performed to develop prognostic models. **RESULTS:** Median OS was 10.8 months. A total of 196 patients (36.7%) had distant progression and 102 patients (19.2%) had local progression. New SBM prognostic indices (SPIs) were devised for OS, DPFS, and LPFS. Graded prognostic assessment, neurologic symptoms (P = 0.01), and tumor volume (P = 0.02) were independently associated with OS. The SPI for OS was defined: unfavorable (OS, 7.3 months), intermediate (OS, 10.6 months), and favorable (OS, 19.8 months). For DPFS, age (P = 0.0029), tumor volume (P = 0.0002), and previous whole-brain radiotherapy (P = 0.027) were prognostic and were used to define SPI for DPFS: favorable (6-month cumulative incidence failure [CIF], 10.9%), intermediate (6-month CIF, 16.7%), and unfavorable (6-month CIF, 26.0%) (P < 0.001). For LPFS, graded prognostic assessment (P = 0.0012) and tumor volume (P = 0.0004) were significant, and defined 2 groups in the LPFS SPI: unfavorable (6-month CIF, 12.3%) and favorable (6-month CIF, 6%) (P < 0.001). **CONCLUSIONS:** This is the largest series of patients with SBM treated with SRS analyzed for OS, LPFS, and DPFS. SPI was devised for end points. Tumor volume had a significant association with all 3 end points. Neurologic symptoms, age, and previous whole-brain radiotherapy were also found to be prognostic.

[158] Gamma Knife radiosurgery for brain metastases from gastrointestinal primary.

Journal of medical imaging and radiation oncology. 2017;61(4):522-527
Page BR, Wang EC, White L, McTyre E, Peiffer A, Alistar A, Mu F, Loganathan A, Bourland JD, Laxton AW, Tatter SB, Chan MD
PMID: 28139076 DOI: 10.1111/1754-9485.12584

INTRODUCTION: In this study, we assessed clinical outcomes of patients with brain metastases from a gastrointestinal (GI) primary cancer and patterns of failure after stereotactic radiosurgery including failure within the radiosurgical volume, distant failure and leptomeningeal failure (LMF). We also assessed other factors associated with the patients' neurologic and extraneural disease that may affect clinical outcomes. **METHODS:** We reviewed our institutional series of 62 consecutive patients with brain metastases treated with stereotactic radiosurgery, which included 17 patients with oesophageal, 44 patients with colorectal and one patient with anal canal primary. The median marginal dose to the radiosurgery

volume was 17 Gy (range 10-24 Gy). Thirteen patients were treated with whole-brain radiotherapy (WBRT) prior to GKS. **RESULTS:** The median dose delivered to the margin of the tumour was 17 Gy (range: 10-24 Gy). The median largest tumour diameter was 2.7 cm (range: 0.60-6.1 cm). The median overall survival (OS) was 7.1 months with a median follow-up of 6.1 months and a range of 0-31.7 months. Freedom from local failure was 86.5% and 62.2% at 6 and 12 months respectively. Freedom from distant failure was 73.2% and 42.2% at 6 and 12 months, respectively, and 40% of patients died of neurologic death. LMF occurred in seven patients, all of whom had colorectal primaries. Multivariate analysis revealed that craniotomy for resection of brain metastasis (HR = 2.63, P < 0.02), an absence of extracranial disease (HR = 2.28, P < 0.03), and prolonged time to distant brain failure (HR = 2.85, P < 0.01) predicted for improved survival. **CONCLUSIONS:** Colorectal cancer metastases tend to have a higher rate of leptomeningeal failure than other types of GI cancer metastases. Radiosurgical management of brain metastases from GI primary represents an acceptable management option. Neurologic death remains problematic.

[159] Stereotactic radiosurgery for focal leptomeningeal disease in patients with brain metastases.

Journal of neuro-oncology. 2017;134(1):139-143

Wolf A, Donahue B, Silverman JS, Chachoua A, Lee JK, Kondziolka D
PMID: 28536993 DOI: 10.1007/s11060-017-2497-6

Leptomeningeal disease (LMD) is well described in patients with brain metastases, presenting symptomatically in approximately 5% of patients. Conventionally, the presence of LMD is an indication for whole brain radiation therapy (WBRT) and not suitable for stereotactic radiosurgery (SRS). The purpose of the study was to evaluate the local control and overall survival of patients who underwent SRS to focal LMD. We reviewed our prospective registry and identified 32 brain metastases patients with LMD, from a total of 465 patients who underwent SRS between 2013 and 2015. Focal LMD was targeted with SRS in 16 patients. The median imaging follow-up time was 7 months. The median volume of LMD was 372 mm³ and the median margin dose was 16 Gy. Five patients underwent prior WBRT. Histology included non-small cell lung (8), breast (5), melanoma (1), gastrointestinal (1) and ovarian cancer (1). Follow-up MR imaging was available for 14 patients. LMD was stable in 5 and partially regressed in 8 patients at follow-up. One patient had progression of LMD with hemorrhage 5 months after SRS. Seven patients developed distant LMD at a median time of 7 months. The median actuarial overall survival from SRS for LMD was 10.0 months. The 6-month and 1-year actuarial overall survival was 60% and 26% respectively. Six patients underwent WBRT after SRS for focal LMD at a median time of 6 months. Overall, focal LMD may be treated successfully with radiosurgery, potentially delaying WBRT in some patients.

[160] Brain metastases in cancer patients attending a Gamma Knife Center: A study from a single institute in Iran.

Asian journal of neurosurgery. 2017;12(3):529-533

Azimi P, Shahzadi S, Bitaraf MA, Azar M, Alikhani M, Zali A, Sadeghi S, Montazeri A
PMID: 28761536 DOI: 10.4103/1793-5482.145564

BACKGROUND: This study was aimed to explore data on brain metastases in cancer patients attending the Iranian Gamma Knife Center. **MATERIALS AND METHODS:** This was a retrospective study. In all 5216 case records of patients who referred to the Iranian Gamma Knife Center for treatment of brain tumors during year 2003-2011 were reviewed. Data were explored to identify patients who developed brain metastases due to cancer and assessed the information as applied to cancer patients including survival analysis. **RESULTS:** Two hundred and twenty patients were identified as having brain metastases due to cancer. The mean age of patients was 54.0 (standard deviation [SD] = 12.7) years. Patients were followed for an average of 7 months after treatment with gamma-knife. The median survival time for different the Graded Prognostic Assessment (GPA) was: GPA: 0-1, 4.0 +/- 0.4 months; GPA: 1.5-2.5, 6.0 +/- 0.7 months; GPA: 3, 9.0 +/- 0.9 months; and GPA: 3.5-4.0, 12.0 +/- 1.8 months and the overall median survival was

7.0 (SD = 0.6) months. **CONCLUSION:** The findings suggest that many cancer patients in Iran might develop brain metastasis. Although, this is not a very high incidence compared with the existing statistics from other countries, there is an urgent need to explore the issue further.

[161] Quality of Life following Stereotactic Radiosurgery for Single and Multiple Brain Metastases.

Neurosurgery. 2017;81(1):147-155

Miller JA, Kotecha R, Barnett GH, Suh JH, Angelov L, Murphy ES, Vogelbaum MA, Mohammadi A, Chao ST
PMID: 28327994 DOI: 10.1093/neuros/nyw166

BACKGROUND: Given the neurological morbidity and poor prognosis associated with brain metastases, it is critical to deliver appropriate therapy while remaining mindful of patient quality of life (QOL). For many patients, stereotactic radiosurgery (SRS) effectively controls intracranial disease, but QOL outcomes have not been characterized. **OBJECTIVE:** To determine the effect of number of brain metastases upon QOL preservation following SRS. **METHODS:** The EuroQol 5 Dimensions questionnaire (EQ-5D) and Patient Health Questionnaire 9 instruments were prospectively collected from a cohort of patients undergoing SRS for brain metastasis between 2008 and 2015. These instruments served as measures of overall QOL and depression. QOL deterioration exceeding the minimum clinically important difference was considered failure. Freedom from 12-month EQ-5D index failure was the primary outcome. **RESULTS:** One hundred and twenty-two SRS treatments (67 patients, 421 lesions) were eligible for inclusion. Intracranial failure (local or distant) occurred following 61% of treatments. Among 421 lesions, 8% progressed locally. Median follow-up was 12 months. **CONCLUSIONS:** Among patients with brain metastasis, QOL preservation must remain paramount as multimodality therapy continues to improve. In the present investigation, 12-month QOL preservation was 79%. However, patients with more than 3 brain metastases were at significantly greater risk for QOL decline.

[162] Repeat stereotactic radiosurgery as salvage therapy for locally recurrent brain metastases previously treated with radiosurgery.

Journal of neurosurgery. 2017;127(1):148-156

McKay WH, McTyre ER, Okoukoni C, Alphonse-Sullivan NK, Ruiz J, Munley MT, Qasem S, Lo HW, Xing F, Laxton AW, Tatter SB, Watabe K, Chan MD
PMID: 27494815 DOI: 10.3171/2016.5.JNS153051

OBJECTIVE: There are a variety of salvage options available for patients with brain metastases who experience local failure after stereotactic radiosurgery (SRS). These options include resection, whole-brain radiation therapy, laser thermoablation, and repeat SRS. There is little data on the safety and efficacy of repeat SRS following local failure of a prior radiosurgical procedure. This study evaluates the clinical outcomes and dosimetric characteristics of patients who experienced tumor recurrence and were subsequently treated with repeat SRS. **METHODS:** Between 2002 and 2015, 32 patients were treated with repeat SRS for local recurrence of >= 1 brain metastasis following initial SRS treatment. The Kaplan-Meier method was used to estimate time-to-event outcomes including overall survival (OS), local failure, and radiation necrosis. Cox proportional hazards analysis was performed for predictor variables of interest for each outcome. Composite dose-volume histograms were constructed for each irradiated lesion, and these were then used to develop a predictive dosimetric model for radiation necrosis. **RESULTS:** Forty-six lesions in 32 patients were re-treated with a second course of SRS after local failure. A median dose of 20 Gy (range 14-22 Gy) was delivered to the tumor margin at the time of repeat SRS. Local control at 1 year was 79% (95% CI 67%-94%). Estimated 1-year OS was 70% (95% CI 55%-88%). Twelve patients had died at the most recent follow-up, with 8/12 patients experiencing neurological death (as described in Patchell et al.). Eleven of 46 (24%) lesions in 11 separate patients treated with repeat SRS were associated with symptomatic radiation necrosis. Freedom from radiation necrosis at 1 year was 71% (95% CI 57%-88%). Analysis of dosimetric data revealed that the volume of a

lesion receiving 40 Gy (V40Gy) was the most predictive factor for the development of radiation necrosis ($p = 0.003$). The following V40Gy thresholds were associated with 10%, 20%, and 50% probabilities of radiation necrosis, respectively: 0.28 cm(3) (95% CI 3%-28%), 0.76 cm(3) (95% CI 9%-39%), 1.60 cm(3) (95% CI 26%-74%). **CONCLUSIONS:** Repeat SRS appears to be an effective salvage option for patients with brain metastases experiencing local failure following initial SRS treatment. This series demonstrates durable local control and, although rates of radiation necrosis are significant, repeat SRS may be indicated for select cases of local disease recurrence. Because the V40Gy is predictive of radiation necrosis, limiting this value during treatment planning may allow for a reduction in radiation necrosis rates.

[163] Prognostic Impact of Histologic Subtype in Non-Small Cell Lung Cancer Patients Treated with Gamma Knife Radiosurgery: Retrospective Analysis of 104 Patients.

Turkish neurosurgery. 2017;27(1):14-21

Aydemir F, Tufan K, Cekinmez M, Kardes O, Sarica FB, Topkan E, Sonmez E, Alkan O, Ugurluer G, Altinors N

PMID: 27593758 DOI: 10.5137/1019-5149.JTN.14831-15.1

AIM: In this study, factors affecting survival, local failure, distant brain failure, whole brain failure and whole-brain radiation therapy (WBRT) free survival according to histological subtypes were investigated in patients with brain metastases from non-small cell lung cancer (NSCLC). **MATERIAL AND METHODS:** Patients with positive pathology reports for adenocarcinoma (ACA) and squamous cell carcinoma (SCC) were included in the study. Seventy-eight ACA and 26 SCC patients were included in the study. Patients with previous history of cerebral metastasis surgery and WBRT were excluded from the study. **RESULTS:** The median survival was calculated as 12.6 months for patients with ACA and 5.9 months for patients with SCC. One-year distant brain failure was calculated as 65.1% in ACA patients and 39.6% in SCC patients. One-year whole brain failure was calculated as 58.1% in ACA patients and 39.6% in SCC patients. The one-year freedom from WBRT rate was calculated as 72.8% in ACA patients and 56.3% in SCC patients. SCC histology was considered as a significant factor in deterioration of overall survival in multivariate analysis. SCC histology, the increase in the number of metastases and RPA class were factors that caused an increase in distant brain failure. Also, SCC histology, the increase in the number of metastases and RPA class were factors that caused an increase in whole brain failure. **CONCLUSION:** SCC histology may be an important prognostic factor for overall survival. Also, due to high distant brain failure rate in SCC histology, WBRT can be added to treatment early.

[164] Stereotactic radiosurgery in the treatment of brain metastases from gynecologic primary cancer.

Journal of radiosurgery and SBRT. 2017;5(1):55-61

Johnston H, McTyre ER, Cramer CK, Lesser GJ, Ruiz J, Bourland JD, Watabe K, Lo HW, Qasem S, Laxton AW, Tatter SB, Chan MD

PMID: 29296463 DOI:

BACKGROUND: Brain metastases from gynecologic primary cancers are rare events, but they can be a cause of morbidity and mortality when they occur. **METHODS:** This is a single institution retrospective study on patients with brain metastases from gynecologic primary cancer who received Gamma Knife stereotactic radiosurgery (SRS). Between 2000 and 2013, a total of 33 patients with brain metastases from gynecologic primary including cervical ($n=2$), endometrial ($n=6$) and ovarian cancers ($n=25$) were treated with SRS at our institution. Electronic medical records were reviewed to determine survival, patterns of failure and cause of death. **RESULTS:** Overall survival at 1, 2 and 5 years for the entire population was 47.1%, 21.7%, and 14.5%, respectively. There was no difference in survival between the primary cancers (log-rank $p = 0.33$). 36.4% patients died of neurologic death. Local failure at 1 and 2 years for the entire population was 10.4% and 14.3%, respectively. There was no difference in local failure between the primary cancers. Distant brain failure at 1, 2 and 5 years for

the entire population was 20.6%, 27.7%, and 31.3%, respectively. On multivariate Cox Proportional Hazards analysis, age was the only predictor of overall survival ($HR = 1.03$, $p = 0.01$). Ovarian cancer patients had decreased risk of distant brain failure ($HR = 0.17$, $p=0.005$), whereas cervical cancer patients had an increased risk of distant brain failure ($HR = 35.7$, $p = 0.001$). **CONCLUSIONS:** SRS represents a feasible treatment option for patients with brain metastases from gynecologic cancer. Younger age is a positive prognostic factor. Ovarian cancer patients have lower risk of distant brain failure.

[165] A Single-Institution Analysis of 126 Patients Treated with Stereotactic Radiosurgery for Brain Metastases.

Frontiers in oncology. 2017;7:90

Harris KB, Corbett MR, Mascarenhas H, Lee KS, Arastu H, Leinweber C, Ju AW
PMID: 28553615 DOI: 10.3389/fonc.2017.00090

BACKGROUND: The objective of this study was to report our institutional experience with Gamma Knife(R) Radiosurgery (GKRS) in the treatment of patients with brain metastases. **METHODS:** Retrospectively collected demographic and clinical data on 126 patients with intracranial metastases were reviewed. The patients in our study underwent GKRS at Vidant Medical Center between 2009 and 2014. Kaplan-Meier curves were used to compare survival based on clinical characteristics for univariate analysis, and a Cox proportional hazards model was used for multivariate analysis. **RESULTS:** The median age of the patient population was 62 years. Medicare patients constituted 51% of our patient cohort and Medicaid patients 15%. The most common tumor histologies were non-small cell lung cancer (50%), breast cancer (12.7%), and melanoma (11.9%). The median overall survival time for all patients was 5.8 months. Patients with breast cancer had the longest median survival time of 9.15 months, while patients with melanoma had the shortest median survival time of 2.86 months. On univariate analysis, the following factors were predictors for improved overall survival, ECOG score 0 or 1 vs. 2 or greater (17.0 vs. 1.8 months, $p < 0.001$), controlled extracranial disease vs. progressive extracranial disease (17.4 vs. 4.6 months, $p = 0.0001$), recursive partitioning analysis Stage I vs. II-III (18.2 vs. 6.2 months, $p < 0.007$), multiple GKRS treatments ($p = 0.002$), prior brain metastasectomy ($p = 0.012$), and prior chemotherapy ($p = 0.021$). Age, ethnicity, gender, previous external beam radiation therapy, number of brain metastases, and hemorrhagic vs. non-hemorrhagic tumors were not predictors of longer median survival time. Number of metastatic brain lesions of 1-3 vs. ≥ 4 ($p = 0.051$) and insurance status of Medicare/Medicaid vs. commercial insurance approached significance (13.7 vs. 6.8 months, $p = 0.08$). On multivariate analysis, ECOG performance status 0-1 ($p < 0.001$), multiple GKRS treatments ($p = 0.003$), and control of extracranial disease ($p = 0.001$) remained significant predictors of survival. **CONCLUSION:** ECOG score, control of extracranial disease, and multiple GKRS treatments are predictors of longer median survival following GKRS in our patient population. GKRS is an effective treatment for brain metastases, but these factors may be considered in patient selection for GKRS.

[166] Distant brain recurrence in patients with five or more newly diagnosed brain metastases treated with focal stereotactic radiotherapy alone.

Journal of radiosurgery and SBRT. 2017;4(4):255-263

Barrett OC, McDonald AM, Thompson JW, Bredel M, McGwin G, Riley KO, Fivash JB

PMID: 28626600 DOI:

BACKGROUND: To assess the clinical outcomes in patients with greater than 4 newly diagnosed brain metastases treated with focal stereotactic radiotherapy alone. **METHODS:** All patients with five or more brain metastases who received focal radiotherapy without whole brain radiation or resection were included in this retrospective analysis. Distant brain failure (DBF), overall survival (OS) and toxicity were reported. **RESULTS:** Thirty-six patients met inclusion with median clinical follow-up of 6.3 months (range: 1.1, 51.4). Twenty-nine patients received stereotactic radiosurgery (SRS) to a median dose of 20 Gy (16-20), and 7 received fractionated stereotactic radiotherapy (FSRT) to a median dose of 30 Gy (25, 30) in

five fractions. The median lesion number and total brain metastases volume was 6 (5, 14) and 1.55 cc (0.12, 32.96), respectively. The Kaplan-Meier estimate of DBF at six-month was 58%, and survival probability at 1 year was 49%. Twenty percent of patients experienced systemic death without CNS relapse. Eight percent experienced grade 3 toxicity with no grade 4 or 5 toxicity. Neither tumor volume nor number predicted DBF. **CONCLUSIONS:** DBF, OS and treatment toxicity were similar to historical controls with fewer than five metastases treated with focal radiation. Focal stereotactic radiotherapy alone without whole brain RT is a reasonable treatment strategy for five or more brain metastases.

[167] Radiosurgery for brainstem metastases with and without whole brain radiotherapy: clinical series and literature review.

Journal of radiation oncology. 2017;6(1):21-30

Murray L, Menard C, Zadeh G, Au K, Bernstein M, Millar BA, Laperriere N, Chung C

PMID: 28367275 DOI: 10.1007/s13566-016-0281-4

OBJECTIVE: The objective of this study was to investigate outcomes for patients with brainstem metastases treated with stereotactic radiosurgery (SRS). **METHODS:** Patients with brainstem metastases treated with SRS between April 2006 and June 2012 were identified from a prospective database. Patient and treatment-related factors were recorded. Kaplan-Meier analysis was used to calculate survival and freedom from local and distant brain progression. Univariate and multivariate Cox regression was used to identify factors important for overall survival. **RESULTS:** In total, 44 patients received SRS for 48 brainstem metastases of whom 33 (75 %) also received whole brain radiotherapy (WBRT): 23 patients (52 %) WBRT prior to SRS, 6 (13.6 %) WBRT concurrently with SRS and 4 (9.0 %) WBRT after SRS. Eight patients received a second course of WBRT at further progression. Median target volume was 1.33 cc (range 0.04-12.17) and median prescribed marginal dose was 15 Gy (range 10-22). There were four cases of local failure, and 6-month and 1-year freedom from local failure was 84.6 and 76.9 %, respectively. Median overall survival (OS) was 5.4 months. There were four cases of radionecrosis, 2 (4.8 %) of which were symptomatic. The absence of external beam brain radiotherapy (predominantly WBRT) showed a trend towards improved OS on univariate analysis. Neither local nor distant brain failure significantly impacted OS. **CONCLUSION:** This retrospective series of patients treated with SRS for brainstem metastases, largely in combination with at least one course of WBRT, demonstrates that this approach is safe and results in good local control. In this cohort, no variables significantly impacted OS, including intracranial control.

[168] Impact of the Number of Metastatic Tumors Treated by Stereotactic Radiosurgery on the Dose to Normal Brain: Implications for Brain Protection.

Stereotactic and functional neurosurgery. 2017;95(5):352-358

Rivers C, Tranquilli M, Prasad S, Winograd E, Plunkett RJ, Fenstermaker RA, Fabiano AJ, Podgorsak MB, Prasad D

PMID: 29017157 DOI: 10.1159/000480666

PURPOSE/OBJECTIVES: The purpose of this study was to evaluate the effect of the number of brain lesions for which stereotactic radiosurgery (SRS) was performed on the dose volume relationships in normal brain. **MATERIALS AND METHODS:** Brain tissue was segmented using the patient's pre-SRS MRI. For each plan, the following data points were recorded: total brain volume, number of lesions treated, volume of brain receiving 8 Gy (V8), V10, V12, and V15. **RESULTS:** A total of 225 Gamma Knife(R) treatments were included in this retrospective analysis. The number of lesions treated ranged from 1 to 29. The isodose for prescription ranged from 40 to 95% (mean 55%). The mean prescription dose to tumor edge was 18 Gy. The mean coverage, selectivity, conformity, and gradient index were 97.5%, 0.63, 0.56, and 3.5, respectively. The mean V12 was 9.5 cm³ (ranging from 0.5 to 59.29). There was no correlation between the number of lesions and brain V8, V12, V10, or V15. There was a direct and statistically significant relationship between the brain volume treated (V8, V10, V12, and V15) and total volume of tumors treated ($p < 0.001$). In our study, the integral dose to the brain exceeded 3 J when the total tumor volume exceeded 25

cm³. **CONCLUSIONS:** The number of metastatic brain lesions treated bears no significant relationship to total brain tissue volume treated when using SRS. The fact that the integral dose to the brain exceeded 3 J when the total tumor volume exceeded 25 cm³ is useful for establishing guidelines. Although standard practice has favored using whole brain radiation therapy in patients with more than 4 lesions, a significant amount of normal brain tissue may be spared by treating these patients with SRS. SRS should be carefully considered in patients with multiple brain lesions, with the emphasis on total brain volume involved rather than the number of lesions to be treated.

[169] Overall survival and the response to radiotherapy among molecular subtypes of breast cancer brain metastases treated with targeted therapies.

Cancer. 2017;123(12):2283-2293

Miller JA, Kotecha R, Ahluwalia MS, Mohammadi AM, Chao ST, Barnett GH, Murphy ES, Vogelbaum MA, Angelov L, Peereboom DM, Suh JH

PMID: 28192598 DOI: 10.1002/cncr.30616

BACKGROUND: The current study was conducted to investigate survival and the response to radiotherapy among patients with molecular subtypes of breast cancer brain metastases treated with or without targeted therapies. **METHODS:** Patients diagnosed with breast cancer brain metastases at a single tertiary care institution were included. The primary outcome was overall survival, whereas secondary outcomes included the cumulative incidences of distant intracranial failure, local failure, and radiation necrosis. Competing risks regression was used to model secondary outcomes. **RESULTS:** Within the study period, 547 patients presented with 3224 brain metastases and met inclusion criteria. Among patients with human epidermal growth factor receptor 2 (HER2)-amplified disease, 80% received HER2 antibodies and 38% received HER2/epidermal growth factor receptor tyrosine kinase inhibitors (TKIs). The median survival was significantly shorter in the basal cohort (8.4 months), and progressively increased in the luminal A (12.3 months), HER2-positive (15.4 months), and luminal B (18.8 months) cohorts ($P < .001$). Among patients with HER2-amplified disease, the median survival was extended with the use of both HER2 antibodies (17.9 months vs 15.1 months; $P = .04$) and TKIs (21.1 months vs 15.4 months; $P = .03$). The 12-month cumulative incidences of local failure among molecular subtypes were 6.0% in the luminal A cohort, 10.3% in the luminal B cohort, 15.4% in the HER2-positive cohort, and 9.9% in the basal cohort ($P = .01$). Concurrent HER2/epidermal growth factor receptor TKIs with stereotactic radiosurgery significantly decreased the 12-month cumulative incidence of local failure from 15.1% to 5.7% ($P < .001$). **CONCLUSIONS:** Molecular subtypes appear to be prognostic for survival and predictive of the response to radiotherapy. TKIs were found to improve survival and local control, and may decrease the rate of distant failure. To preserve neurocognition, these results support a paradigm of upfront radiosurgery and HER2-directed therapy in the HER2-amplified population, reserving whole-brain radiotherapy for salvage. *Cancer* 2017;123:2283-2293. (c) 2017 American Cancer Society.

[170] Three or More Courses of Stereotactic Radiosurgery for Patients with Multiply Recurrent Brain Metastases.

Neurosurgery. 2017;80(6):871-879

Kotecha R, Damico N, Miller JA, Suh JH, Murphy ES, Reddy CA, Barnett GH, Vogelbaum MA, Angelov L, Mohammadi AM, Chao ST

PMID: 28327948 DOI: 10.1093/neuros/nyw147

BACKGROUND: Although patients with brain metastasis are treated with primary stereotactic radiosurgery (SRS), the use of salvage therapies and their consequence remains understudied. **OBJECTIVE:** To study the intracranial recurrence patterns and salvage therapies for patients who underwent multiple SRS courses. **METHODS:** A retrospective review was performed of 59 patients with brain metastases who underwent ≥ 3 SRS courses for new lesions. Cox regression analyzed factors predictive for overall survival. **RESULTS:** The median age at diagnosis was 52 years. Over time, patients underwent a median of 3 courses of SRS (range: 3-8) to a total of 765 different brain metastases. The

6-month risk of distant intracranial recurrence after the first SRS treatment was 64% (95% confidence interval: 52%-77%). Overall survival was 40% (95% confidence interval: 28%-53%) at 24 months. Only 24 patients (41%) had a decline in their Karnofsky Performance Status ≤ 70 at last office visit. Quality of life was preserved among 77% of patients at 12 months, with 45% experiencing clinically significant improvement during clinical follow-up. Radiation necrosis developed in 10 patients (17%). On multivariate analysis, gender (males, Hazard Ratio [HR]: 2.0, $P < .05$), Karnofsky Performance Status ≤ 80 (HR 3.2, $P < .001$), extracranial metastases (HR: 3.6, $P < .001$), and a distant intracranial recurrence ≤ 3 months from initial to repeat SRS (HR: 3.8, $P < .001$) were associated with a poorer survival.

CONCLUSION: In selected patients, performing ≥ 3 SRS courses controls intracranial disease. Patients may need salvage SRS for distant intracranial relapse, but focal retreatments are associated with modest toxicity, do not appear to negatively affect a patient's performance status, and help preserve quality of life.

[171] Estimating Survival in Patients With Lung Cancer and Brain Metastases: An Update of the Graded Prognostic Assessment for Lung Cancer Using Molecular Markers (Lung-molGPA).

JAMA oncology. 2017;3(6):827-831

Sperduto PW, Yang TJ, Beal K, Pan H, Brown PD, Bangdiwala A, Shanley R, Yeh N, Gaspar LE, Braunstein S, Sneed P, Boyle J, Kirkpatrick JP, Mak KS, Shih HA, Engelman A, Roberge D, Arvold ND, Alexander B, Awad MM, Contessa J, Chiang V, Hardie J, Ma D, Lou E, Sperduto W, Mehta MP
PMID: 27892978 DOI: 10.1001/jamaoncol.2016.3834

Importance: Lung cancer is the leading cause of cancer-related mortality in the United States and worldwide. As systemic therapies improve, patients with lung cancer live longer and thus are at increased risk for brain metastases. Understanding how prognosis varies across this heterogeneous patient population is essential to individualize care and design future clinical trials. **OBJECTIVE:** To update the current Diagnosis-Specific Graded Prognostic Assessment (DS-GPA) for patients with non-small-cell lung cancer (NSCLC) and brain metastases. The DS-GPA is based on data from patients diagnosed between 1985 and 2005, and we set out to update it by incorporating more recently reported gene and molecular alteration data for patients with NSCLC and brain metastases. This new index is called the Lung-molGPA. Design, Setting, and Participants: This is a multi-institutional retrospective database analysis of 2186 patients diagnosed between 2006 and 2014 with NSCLC and newly diagnosed brain metastases. The multivariable analyses took place between December 2015 and May 2016, and all prognostic factors were weighted for significance by hazard ratios. Significant factors were included in the updated Lung-molGPA prognostic index. Main Outcomes and Measures: The main outcome was survival. Multiple Cox regression was used to select and weight prognostic factors in proportion to their hazard ratios. Log rank tests were used to compare adjacent classes and to compare overall survival for adenocarcinoma vs nonadenocarcinoma groups. **RESULTS:** The original DS-GPA was based on 4 factors found in 1833 patients with NSCLC and brain metastases diagnosed between 1985 and 2005: patient age, Karnofsky Performance Status, extracranial metastases, and number of brain metastases. The patients studied for the creation of the DS-GPA had a median survival of 7 months from the time of initial treatment of brain metastases. To design the updated Lung-molGPA, we analyzed data from 2186 patients from 2006 through 2014 with NSCLC and newly diagnosed brain metastases (1521 adenocarcinoma and 665 nonadenocarcinoma). Significant prognostic factors included the original 4 factors used in the DS-GPA index plus 2 new factors: EGFR and ALK alterations in patients with adenocarcinoma (mutation status was not routinely tested for nonadenocarcinoma). The overall median survival for the cohort in the present study was 12 months, and those with NSCLC-adenocarcinoma and Lung-molGPA scores of 3.5 to 4.0 had a median survival of nearly 4 years. **CONCLUSIONS AND RELEVANCE:** In recent years, patient survival and physicians' ability to predict survival in NSCLC with brain metastases has improved significantly. The updated Lung-molGPA incorporating gene alteration data into the DS-GPA is a user-friendly tool that may facilitate clinical decision making and appropriate stratification of future clinical trials.

[172] Discovery of additional brain metastases on the day of stereotactic radiosurgery: risk factors and outcomes.

Journal of neurosurgery. 2017;126(6):1756-1763

Garcia MA, Lazar A, Duriseti S, Raleigh DR, Hess CP, Fogh SE, Barani IJ, Nakamura JL, Larson DA, Theodosopoulos P, McDermott M, Sneed PK, Braunstein S
PMID: 27367235 DOI: 10.3171/2016.4.JNS152319

OBJECTIVE: High-resolution double-dose gadolinium-enhanced Gamma Knife (GK) radiosurgery-planning MRI (GK MRI) on the day of GK treatment can detect additional brain metastases undiagnosed on the prior diagnostic MRI scan (dMRI), revealing increased intracranial disease burden on the day of radiosurgery, and potentially necessitating a reevaluation of appropriate management. The authors identified factors associated with detecting additional metastases on GK MRI and investigated the relationship between detection of additional metastases and postradiosurgery patient outcomes. **METHODS:** The authors identified 326 patients who received GK radiosurgery at their institution from 2010 through 2013 and had a prior dMRI available for comparison of numbers of brain metastases. Factors predictive of additional brain metastases on GK MRI were investigated using logistic regression analysis. Overall survival was estimated by Kaplan-Meier method, and postradiosurgery distant intracranial failure was estimated by cumulative incidence measures. Multivariable Cox proportional hazards model and Fine-Gray regression modeling assessed potential risk factors of overall survival and distant intracranial failure, respectively. **RESULTS:** The mean numbers of brain metastases (SD) on dMRI and GK MRI were 3.4 (4.2) and 5.8 (7.7), respectively, and additional brain metastases were found on GK MRI in 48.9% of patients. Frequencies of detecting additional metastases for patients with 1, 2, 3-4, and more than 4 brain metastases on dMRI were 29.5%, 47.9%, 55.9%, and 79.4%, respectively ($p < 0.001$). An index brain metastasis with a diameter greater than 1 cm on dMRI was inversely associated with detecting additional brain metastases, with an adjusted odds ratio of 0.57 (95% CI 0.4-0.9, $p = 0.02$). The median time between dMRI and GK MRI was 22 days (range 1-88 days), and time between scans was not associated with detecting additional metastases. Patients with additional brain metastases did not have larger total radiosurgery target volumes, and they rarely had an immediate change in management (abortion of radiosurgery or addition of whole-brain radiation therapy) due to detection of additional metastases. Patients with additional metastases had a higher incidence of distant intracranial failure than those without additional metastases ($p = 0.004$), with an adjusted subdistribution hazard ratio of 1.4 (95% CI 1.0-2.0, $p = 0.04$). Significantly worse overall survival was not detected for patients with additional brain metastases on GK MRI (log-rank $p = 0.07$), with the relative adjusted hazard ratio of 1.07, (95% CI 0.81-1.41, $p = 0.65$). **CONCLUSIONS:** Detecting additional brain metastases on GK MRI is strongly associated with the number of brain metastases on dMRI and inversely associated with the size of the index brain metastasis. The discovery of additional brain metastases at time of GK radiosurgery is very unlikely to lead to aborting radiosurgery but is associated with a higher incidence of distant intracranial failure. However, there is not a significant difference in survival. **CLASSIFICATION OF EVIDENCE** Type of question: prognostic; study design: retrospective cohort trial; evidence: Class IV.

[173] Optimal dose and volume for postoperative radiotherapy in brain oligometastases from lung cancer: a retrospective study.

Radiation oncology journal. 2017;35(2):153-162

Chung SY, Chang JH, Kim HR, Cho BC, Lee CG, Suh CO

PMID: 28712276 DOI: 10.3857/roj.2017.00094

PURPOSE: To evaluate intracranial control after surgical resection according to the adjuvant treatment received in order to assess the optimal radiotherapy (RT) dose and volume. **MATERIALS AND METHODS:** Between 2003 and 2015, a total of 53 patients with brain oligometastases from non-small cell lung cancer (NSCLC) underwent metastasectomy. The patients were divided into three groups according to the adjuvant treatment received: whole brain radiotherapy (WBRT) +/- boost (WBRT +/- boost group, $n = 26$), local RT/Gamma Knife surgery (local RT group, $n = 14$), and

the observation group (n = 13). The most commonly used dose schedule was WBRT (25 Gy in 10 fractions, equivalent dose in 2 Gy fractions [EQD2] 26.04 Gy) with tumor bed boost (15 Gy in 5 fractions, EQD2 16.25 Gy). **RESULTS:** The WBRT +/- boost group showed the lowest 1-year intracranial recurrence rate of 30.4%, followed by the local RT and observation groups, at 66.7%, and 76.9%, respectively (p = 0.006). In the WBRT +/- boost group, there was no significant increase in the 1-year new site recurrence rate of patients receiving a lower dose of WBRT (EQD2) <27 Gy compared to that in patients receiving a higher WBRT dose (p = 0.553). The 1-year initial tumor site recurrence rate was lower in patients receiving tumor bed dose (EQD2) of >=42.3 Gy compared to those receiving <42.3 Gy, although the difference was not significant (p = 0.347). **CONCLUSIONS:** Adding WBRT after resection of brain oligometastases from NSCLC seems to enhance intracranial control. Furthermore, combining lower-dose WBRT with a tumor bed boost may be an attractive option.

[174] The risk of radiation necrosis following stereotactic radiosurgery with concurrent systemic therapies.

Journal of neuro-oncology. 2017;133(2):357-368

Kim JM, Miller JA, Kotecha R, Xiao R, Juloori A, Ward MC, Ahluwalia MS, Mohammadi AM, Peereboom DM, Murphy ES, Suh JH, Barnett GH, Vogelbaum MA, Angelov L, Stevens GH, Chao ST

PMID: 28434110 DOI: 10.1007/s11060-017-2442-8

To investigate late toxicity among patients with newly-diagnosed brain metastases undergoing stereotactic radiosurgery (SRS) with concurrent systemic therapies with or without whole-brain radiation therapy (WBRT). Patients with newly-diagnosed brain metastasis who underwent SRS at a single tertiary-care institution from 1997 to 2015 were eligible for inclusion. The class and timing of all systemic therapies were collected for each patient. The primary outcome was the cumulative incidence of radiographic radiation necrosis (RN). Multivariable competing risks regression was used to adjust for confounding. During the study period, 1650 patients presented with 2843 intracranial metastases. Among these, 445 patients (27%) were treated with SRS and concurrent systemic therapy. Radiographic RN developed following treatment of 222 (8%) lesions, 120 (54%) of which were symptomatic. The 12-month cumulative incidences of RN among lesions treated with and without concurrent therapies were 6.6 and 5.3%, respectively (p = 0.14). Concurrent systemic therapy was associated with a significantly increased rate of RN among lesions treated with upfront SRS and WBRT (8.7 vs. 3.7%, p = 0.04). In particular, concurrent targeted therapies significantly increased the 12-month cumulative incidence of RN (8.8 vs. 5.3%, p < 0.01). Among these therapies, significantly increased rates of RN were observed with VEGFR tyrosine kinase inhibitors (TKIs) (14.3 vs. 6.6%, p = 0.04) and EGFR TKIs (15.6 vs. 6.0%, p = 0.04). Most classes of systemic therapies may be safely delivered concurrently with SRS in the management of newly-diagnosed brain metastases. However, the rate of radiographic RN is significantly increased with the addition of concurrent systemic therapies to SRS and WBRT.

[175] Optimal implantation of Ommaya reservoirs for cystic metastatic brain tumors preceding Gamma Knife radiosurgery.

Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2017;39:199-202

Oshima A, Kimura T, Akabane A, Kawai K

PMID: 28117259 DOI: 10.1016/j.jocn.2016.12.042

INTRODUCTION: Although Ommaya reservoir implantation is effective in reducing the target volume of cystic brain metastases preceding stereotactic radiosurgery, adequate volume reduction cannot be achieved in some cases, and the factors leading to failure in volume reduction have not been clearly identified. In this study, we investigated the factors leading to failure in volume reduction after use of the Ommaya reservoir. **MATERIALS AND METHODS:** Between December 2007 and February 2015, 38 consecutive patients with 40 cystic metastases underwent Ommaya reservoir implantation at our institution. The patient characteristics, treatment parameters, and all available clinical and neuroimaging follow-ups were analyzed retrospectively. **RESULTS:** The rate of

volume reduction was significantly related to the location of the tube tip inside the cyst. By placing the tip at or near the center, 58.7% reduction was achieved, whereas reduction of 42.6% and 7.7% occurred with deep and shallow tip placement, respectively (p=0.011). Although there was no additional surgery in the center placement group, additional surgeries were performed in 5 out of the 23 deep and shallow cases due to inadequate volume reduction. No other factors were correlated with successful volume reduction. **CONCLUSION:** For adequate volume reduction using the Ommaya reservoir in the treatment of cystic brain metastases prior to stereotactic radiosurgery, the tip of the reservoir tube should be placed at the center of the cyst.

[176] Treatment options for patients with brain metastases from EGFR/ALK-driven lung cancer.

Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2017;123(2):195-202

Doherty MK, Korpanty GJ, Tomasini P, Alizadeh M, Jao K, Labbe C, Mascaux CM, Martin P, Kamel-Reid S, Tsao MS, Pintilie M, Liu G, Bradbury PA, Feld R, Leigh NB, Chung C, Shepherd FA

PMID: 28363487 DOI: 10.1016/j.radonc.2017.03.007

INTRODUCTION: Brain metastases in EGFR/ALK-driven NSCLC frequently pose treatment dilemmas. Tyrosine kinase inhibitors (TKIs) can control extracranial disease, but radiotherapy is often required for intracranial control. We aimed to evaluate the impact of first-line whole brain radiotherapy (WBRT), stereotactic radiotherapy (SRS) or TKI alone on outcomes of patients with brain metastases from EGFR/ALK-driven NSCLC. **METHODS:** This single center retrospective review included 184 patients with brain metastases from EGFR/ALK-driven NSCLC, and analyzed effect of treatment choice on time to intracranial progression (TTIP) and overall survival (OS). **RESULTS:** First-line treatment for brain metastases consisted of WBRT in 120 patients, SRS in 37 and TKI alone in 27. WBRT-treated patients had more brain metastases, and more baseline symptoms. Median TTIP was longer in the WBRT group at 50.5months than SRS or TKI groups at 12 and 15months (p=0.0038). No significant difference was seen in median OS: 21.6months in the WBRT group, 23.9months in the SRS group and 22.6months in the TKI group (p=0.67). In multivariable analysis, age>65years (HR 2.2, p=0.0014), greater number of brain metastases (HR 2.48, p=0.0002) and greater number of extracranial metastatic sites (2 vs 0-1 HR=2.05, p=0.014 and 3+ vs 0-1 HR=2.95, p=0.0001) were associated with shorter OS. No independent effect was seen from first-line CNS treatment choice. **CONCLUSIONS:** First-line WBRT for brain metastases from EGFR/ALK-driven NSCLC was associated with longer TTIP than SRS or TKI alone, with no difference in OS. These results could support deferral of WBRT until intracranial progression in selected patients who are closely monitored.

[177] Brain Metastasis Velocity: A Novel Prognostic Metric Predictive of Overall Survival and Freedom From Whole-Brain Radiation Therapy After Distant Brain Failure Following Upfront Radiosurgery Alone.

International journal of radiation oncology, biology, physics. 2017;98(1):131-141

Farris M, McTyre ER, Cramer CK, Hughes R, Randolph DM 2nd, Ayala-Peacock DN, Bourland JD, Ruiz J, Watabe K, Laxton AW, Tatter SB, Zhou X, Chan MD

PMID: 28586952 DOI: 10.1016/j.ijrobp.2017.01.201

PURPOSE: Prior statistical models attempted to identify risk factors for time to distant brain failure (DBF) or time to salvage whole-brain radiation therapy (WBRT) to predict the benefit of early WBRT versus stereotactic radiosurgery (SRS) alone. We introduce a novel clinical metric, brain metastasis velocity (BMV), for predicting clinical outcomes after initial DBF following upfront SRS alone. **METHODS AND MATERIALS:** BMV was defined as the cumulative number of new brain metastases that developed over time since first SRS in years. Patients were classified by BMV into low-, intermediate-, and high-risk groups, consisting of <4, 4 to 13, and >13 new metastases per year, respectively. Histology, number of metastases at the time of first SRS, and systemic disease status were assessed for effect on BMV. **RESULTS:** Of 737 patients treated at our institution with

upfront SRS without WBRT, 286 had ≥ 1 DBF event. A lower BMV predicted for improved overall survival (OS) following initial DBF (log-rank $P < .0001$). Median OS for the low, intermediate, and high BMV groups was 12.4 months (95% confidence interval [CI], 10.4-16.9 months), 8.2 months (95% CI, 5.0-9.7 months), and 4.3 months (95% CI, 2.6-6.7 months), respectively. Multivariate analysis showed that BMV remained the dominant predictor of OS, with a hazard ratio of 2.75 for the high BMV group (95% CI, 1.94-3.89; $P < .0001$) and a hazard ratio of 1.65 for the intermediate BMV group (95% CI, 1.18-2.30; $P < .004$). A lower BMV was associated with decreased rates of salvage WBRT ($P = .02$) and neurologic death ($P = .008$). Factors predictive for a higher BMV included ≥ 2 initial brain metastases ($P = .004$) and melanoma histology ($P = .008$). **CONCLUSIONS:** BMV is a novel metric associated with OS, neurologic death, and need for salvage WBRT after initial DBF following upfront SRS alone.

[178] The Effects of smoking status and smoking history on patients with brain metastases from lung cancer.

Cancer medicine. 2017;6(5):944-952

Shenker RF, McTyre ER, Ruiz J, Weaver KE, Cramer C, Alphonse-Sullivan NK, Farris M, Petty WJ, Bonomi MR, Watabe K, Laxton AW, Tatter SB, Warren GW, Chan MD
PMID: 28401684 DOI: 10.1002/cam4.1058

There is limited data on the effects of smoking on lung cancer patients with brain metastases. This single institution retrospective study of patients with brain metastases from lung cancer who received stereotactic radiosurgery assessed whether smoking history is associated with overall survival, local control, rate of new brain metastases (brain metastasis velocity), and likelihood of neurologic death after brain metastases. Patients were stratified by adenocarcinoma versus nonadenocarcinoma histologies. Kaplan-Meier analysis was performed for survival endpoints. Competing risk analysis was performed for neurologic death analysis to account for risk of nonneurologic death. Separate linear regression and multivariate analyses were performed to estimate the brain metastasis velocity. Of 366 patients included in the analysis, the median age was 63, 54% were male and, 60% were diagnosed with adenocarcinoma. Current smoking was reported by 37% and 91% had a smoking history. Current smoking status and pack-year history of smoking had no effect on overall survival. There was a trend for an increased risk of neurologic death in nonadenocarcinoma patients who continued to smoke (14%, 35%, and 46% at 6/12/24 months) compared with patients who did not smoke (12%, 23%, and 30%, $P = 0.053$). Cumulative pack years smoking was associated with an increase in neurologic death for nonadenocarcinoma patients (HR = 1.01, CI: 1.00-1.02, $P = 0.046$). Increased pack-year history increased brain metastasis velocity in multivariate analysis for overall patients ($P = 0.026$). Current smokers with nonadenocarcinoma lung cancers had a trend toward greater neurologic death than nonsmokers. Cumulative pack years smoking is associated with a greater brain metastasis velocity.

[179] Predictors of neurologic and nonneurologic death in patients with brain metastasis initially treated with upfront stereotactic radiosurgery without whole-brain radiation therapy.

Neuro-oncology. 2017;19(4):558-566

McTyre ER, Johnson AG, Ruiz J, Isom S, Lucas JT Jr, Hinson WH, Watabe K, Laxton AW, Tatter SB, Chan MD

PMID: 27571883 DOI: 10.1093/neuonc/now184

BACKGROUND: In this study we attempted to discern the factors predictive of neurologic death in patients with brain metastasis treated with upfront stereotactic radiosurgery (SRS) without whole brain radiation therapy (WBRT) while accounting for the competing risk of nonneurologic death. **METHODS:** We performed a retrospective single-institution analysis of patients with brain metastasis treated with upfront SRS without WBRT. Competing risks analysis was performed to estimate the subdistribution hazard ratios (HRs) for neurologic and nonneurologic death for predictor variables of interest. **RESULTS:** Of 738 patients treated with upfront SRS alone, neurologic death occurred in 226 (30.6%), while nonneurologic death occurred in 309 (41.9%). Multivariate competing risks analysis

identified an increased hazard of neurologic death associated with diagnosis-specific graded prognostic assessment (DS-GPA) ≤ 2 ($P = .005$), melanoma histology ($P = .009$), and increased number of brain metastases ($P < .001$), while there was a decreased hazard associated with higher SRS dose ($P = .004$). Targeted agents were associated with a decreased HR of neurologic death in the first 1.5 years ($P = .04$) but not afterwards. An increased hazard of nonneurologic death was seen with increasing age ($P = .03$), nonmelanoma histology ($P < .001$), presence of extracranial disease ($P < .001$), and progressive systemic disease ($P = .004$). **CONCLUSIONS:** Melanoma, DS-GPA, number of brain metastases, and SRS dose are predictive of neurologic death, while age, nonmelanoma histology, and more advanced systemic disease are predictive of nonneurologic death. Targeted agents appear to delay neurologic death.

[180] Fractionated stereotactic radiotherapy for metastatic brain tumors that recurred after gamma knife radiosurgery results in acceptable toxicity and favorable local control.

International journal of clinical oncology. 2017;22(2):250-256

Miyakawa A, Shibamoto Y, Takemoto S, Serizawa T, Otsuka S, Hirai T
PMID: 27826659 DOI: 10.1007/s10147-016-1058-x

BACKGROUND: To treat local recurrence of brain metastases after gamma knife radiosurgery (GKS), we have used fractionated stereotactic radiotherapy (SRT). The purpose of this study was to evaluate the efficacy and toxicity of SRT in these patients. **METHODS:** Fifty locally recurrent metastatic brain tumors in 47 patients were treated with SRT. The median prescribed dose of GKS was 20 Gy at the periphery. The median interval between the GKS (the last session in cases in which multiple GKS procedures were performed) and recurrence was 7.5 (range 1-33) months. Several dose-fractionation protocols were used for SRT, depending on the size and location of the tumor and previous GKS dose. The median prescribed dose of the SRT at the isocenter was 30 Gy with a median of ten fractions. **RESULTS:** Among the 50 lesions treated with SRT, 26 did not recur locally before the patient's death or the last follow-up examination, and 24 recurred locally. The median follow-up period for the surviving patients was 24 months after the first GKS procedure, and the overall survival rate was 80% at 1 year and 57% at 2 years. The median time to local re-recurrence after the SRT (16 months) was significantly longer than the median interval between the last GKS and recurrence (7.5 months; $P < 0.001$). Only two patients developed \geq grade 2 radiation necrosis. **CONCLUSIONS:** Stereotactic radiotherapy appeared to be an effective treatment for recurrent metastatic brain tumors and yielded relatively good local control. The associated adverse events were generally acceptable.

[181] Predictive factors of early distant brain failure after gamma knife radiosurgery alone in patients with brain metastases of non-small-cell lung cancer.

Journal of neuro-oncology. 2017;132(2):333-340

Na YC, Jung HH, Kim HR, Cho BC, Chang JW, Park YG, Chang WS
PMID: 28074321 DOI: 10.1007/s11060-017-2373-4

The objective of this study was to elucidate the predictive factors for early distant brain failure in patients with brain metastases of non-small-cell lung cancer (NSCLC) who were treated with gamma knife radiosurgery (GKRS) without previous whole-brain radiotherapy (WBRT) or surgery. We retrospectively reviewed clinical and imaging data of 459 patients with brain metastases of NSCLC who underwent GKRS from June 2008 to December 2013. The primary end-point was early distant brain failure, defined as the detection of newly developed metastatic lesions on magnetic resonance imaging (MRI) 3 months after GKRS. Factors such as tumor pathology subtype, concurrent systemic chemotherapy, epidermal growth factor receptor (EGFR) mutation status, use of EGFR tyrosine kinase inhibitors (TKIs), systemic disease status, presence of a metastatic lesion only in delayed MRI, and volume and number of metastases were analyzed. There were no statistically significant differences with respect to pathologic subtype, concurrent systemic chemotherapy, EGFR mutation, and early distant brain failure. Patients treated with EGFR-TKIs ($p = 0.004$), with a stable systemic disease status

($p = 0.028$) and 3 or fewer brain lesions ($p = 0.000$) experienced a significantly lower incidence of early distant brain failure. This study suggests that GKRS alone could be considered for patients treated with EGFR-TKIs who have a stable systemic disease status and 3 or fewer brain lesions. WBRT should be considered for other patients.

[182] Quality of life is maintained using Gamma Knife radiosurgery: a prospective study of a brain metastases patient cohort.

Journal of neurosurgery. 2017;126(3):708-725

Skeie BS, Eide GE, Flatebo M, Heggdal JI, Larsen E, Bragstad S, Pedersen PH, Enger PO

PMID: 27058206 DOI: 10.3171/2015.10.JNS15801

OBJECTIVE: Gamma Knife radiosurgery (GKRS) is increasingly used in the management of brain metastases (BMs), but few studies have evaluated how GKRS impacts quality of life (QOL). The aim of this study was to monitor QOL as the primary end point following GKRS in a patient cohort with BM. **METHODS:** The study included 97 consecutive patients with 1-6 BMs treated with GKRS between May 2010 and September 2011. QOL was assessed at baseline and at 1, 3, 6, 9, and 12 months postoperatively using the Functional Assessment of Cancer Therapy-Brain (FACT-BR) questionnaire with the brain cancer subscale (BRCS) questionnaire. Factors predicting QOL were identified by mixed linear regression analyses. Local control and toxicity were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) and the European Organisation for Research and Treatment/Radiation Therapy Oncology Group (EORTC/RTOG) criteria of late effects, respectively. **RESULTS:** Compliance was high from baseline (97%) to 12-month follow-up (78%). Mean BRCS scores remained high during follow-up: they improved in 66% of patients and remained unchanged in 6% at 9 months. Local control ($p = 0.018$), improved symptoms ($p = 0.005$), and stable extracerebral disease ($p = 0.001$) correlated with high QOL-BRCS score. High baseline recursive partitioning analysis class predicted improved QOL ($p = 0.031$), whereas high Karnofsky Performance Scale score ($p = 0.017$), asymptomatic BMs ($p = 0.001$), and no cognitive deficits ($p = 0.033$) or seizures ($p = 0.040$) predicted high, stable QOL-BRCS during the 12-month follow-up. **CONCLUSIONS:** QOL remained stable for up to 12 months following GKRS for the total cohort. High QOL was reported if local control occurred, cerebral symptoms improved/stabilized, or the need for steroids declined, which all reflected successful GKRS. Conversely, low QOL accompanied progression of intra- and extracerebral disease. Based on the study findings, GKRS appears to be a safe and effective treatment option for patients with BMs.

[183] Stereotactic radiosurgery for intracranial hemangiopericytomas: a multicenter study.

Journal of neurosurgery. 2017;126(3):744-754

Cohen-Inbar O, Lee CC, Mousavi SH, Kano H, Mathieu D, Meola A, Nakaji P, Honea N, Johnson M, Abbassy M, Mohammadi AM, Silva D, Yang HC, Grills I, Kondziolka D, Barnett GH, Lunsford LD, Sheehan J

PMID: 27104850 DOI: 10.3171/2016.1.JNS152860

OBJECTIVE: Hemangiopericytomas (HPCs) are rare tumors widely recognized for their aggressive clinical behavior, high recurrence rates, and distant and extracranial metastases even after a gross-total resection. The authors report a large multicenter study, through the International Gamma Knife Research Foundation (IGKRF), reviewing management and outcome following stereotactic radiosurgery (SRS) for recurrent or newly discovered HPCs. **METHODS:** Eight centers participating in the IGKRF participated in this study. A total of 90 patients harboring 133 tumors were identified. Patients were included if they had a histologically diagnosed HPC managed with SRS during the period 1988-2014 and had a minimum of 6 months' clinical and radiological follow-up. A de-identified database was created. The patients' median age was 48.5 years (range 13-80 years). Prior treatments included embolization ($n = 8$), chemotherapy ($n = 2$), and fractionated radiotherapy ($n = 34$). The median tumor volume at the time of SRS was 4.9 cm³ (range 0.2-42.4 cm³). WHO Grade II (typical) HPCs formed 78.9%

of the cohort ($n = 71$). The median margin and maximum doses delivered were 15 Gy (range 2.8-24 Gy) and 32 Gy (range 8-51 Gy), respectively. The median clinical and radiographic follow-up periods were 59 months (range 6-190 months) and 59 months (range 6-183 months), respectively. Prognostic variables associated with local tumor control and post-SRS survival were evaluated using Cox univariate and multivariate analysis. Actuarial survival after SRS was analyzed using the Kaplan-Meier method. **RESULTS:** Imaging studies performed at last follow-up demonstrated local tumor control in 55% of tumors and 62.2% of patients. New remote intracranial tumors were found in 27.8% of patients, and 24.4% of patients developed extracranial metastases. Adverse radiation effects were noted in 6.7% of patients. During the study period, 32.2% of the patients ($n = 29$) died. The actuarial overall survival was 91.5%, 82.1%, 73.9%, 56.7%, and 53.7% at 2, 4, 6, 8, and 10 years, respectively, after initial SRS. Local progression-free survival (PFS) was 81.7%, 66.3%, 54.5%, 37.2%, and 25.5% at 2, 4, 6, 8, and 10 years, respectively, after initial SRS. In our cohort, 32 patients underwent 48 repeat SRS procedures for 76 lesions. Review of these 76 treated tumors showed that 17 presented as an in-field recurrence and 59 were defined as an out-of-field recurrence. Margin dose greater than 16 Gy ($p = 0.037$) and tumor grade ($p = 0.006$) were shown to influence PFS. The development of extracranial metastases was shown to influence overall survival ($p = 0.029$) in terms of PFS; repeat (multiple) SRS showed additional benefit. **CONCLUSIONS:** SRS provides a reasonable rate of local tumor control and a low risk of adverse effects. It also leads to neurological stability or improvement in the majority of patients. Long-term close clinical and imaging follow-up is necessary due to the high probability of local recurrence and distant metastases. Repeat SRS is often effective for treating new or recurrent HPCs.

[184] BRAF V600E mutation and BRAF kinase inhibitors in conjunction with stereotactic radiosurgery for intracranial melanoma metastases.

Journal of neurosurgery. 2017;126(3):726-734

Xu Z, Lee CC, Ramesh A, Mueller AC, Schlesinger D, Cohen-Inbar O, Shih HH, Sheehan JP

PMID: 27203149 DOI: 10.3171/2016.2.JNS1633

OBJECTIVE: Recent advancements in molecular biology have identified the BRAF mutation as a common mutation in melanoma. The wide use of BRAF kinase inhibitor (BRAFi) in patients with metastatic melanoma has been established. The objective of this study was to examine the impact of BRAF mutation status and use of BRAFi in conjunction with stereotactic radiosurgery (SRS). **METHODS:** This was a single-center retrospective study. Patient's charts and electronic records were reviewed for date of diagnosis of primary malignancy, BRAF mutation status, chemotherapies used, date of the diagnosis of CNS metastases, date of SRS, survival, local tumor control after SRS, and adverse events. Patients were divided into 3 groups: Group A, those with mutant BRAF without BRAFi treatment (13 patients); Group B, those with mutant BRAF with BRAFi treatment (17 patients); and Group C, those with wild-type BRAF (35 patients). Within a cohort of 65 patients with the known BRAF mutation status and treated with SRS between 2010 and 2014, 436 individual brain metastases (BMs) were identified. Kaplan-Meier methodology was then used to compare survival based on each binary parameter. **RESULTS:** Median survival times after the diagnosis of melanoma BM and after SRS were favorable in patients with a BRAF mutation and treated with SRS in conjunction with BRAFi (Group B) compared with the patients with wild-type BRAF (Group C, 23 vs 8 months and 13 vs 5 months, respectively; $p < 0.01$, log-rank test). SRS provided a local tumor control rate of 89.4% in the entire cohort of patients. Furthermore, the local control rate was improved in the patients treated with SRS in conjunction with BRAFi (Group B) compared with patients with wild-type (Group C) or with BRAF mutation but no BRAFi (Group A) as an adjunct treatment for BMs. **CONCLUSIONS:** BRAF mutation status appears to play an important role as a potent prognostic factor in patients harboring melanoma BM. BRAFi in conjunction with SRS may benefit this group of patients in terms of BM survival and SRS with an acceptable safety profile.

[185] Impact of the radiosurgery prescription dose on the local control of small (2 cm or smaller) brain metastases.

Journal of neurosurgery. 2017;126(3):735-743

Mohammadi AM, Schroeder JL, Angelov L, Chao ST, Murphy ES, Yu JS, Neyman G, Jia X, Suh JH, Barnett GH, Vogelbaum MA
PMID: 27231978 DOI: 10.3171/2016.3.JNS153014

OBJECTIVE: The impact of the stereotactic radiosurgery (SRS) prescription dose (PD) on local progression and radiation necrosis for small (≤ 2 cm) brain metastases was evaluated. **METHODS:** An institutional review board-approved retrospective review was performed on 896 patients with brain metastases ≤ 2 cm (3034 tumors) who were treated with 1229 SRS procedures between 2000 and 2012. Local progression and/or radiation necrosis were the primary end points. Each tumor was followed from the date of radiosurgery until one of the end points was reached or the last MRI follow-up. Various criteria were used to differentiate tumor progression and radiation necrosis, including the evaluation of serial MRIs, cerebral blood volume on perfusion MR, FDG-PET scans, and, in some cases, surgical pathology. The median radiographic follow-up per lesion was 6.2 months. **RESULTS:** The median patient age was 56 years, and 56% of the patients were female. The most common primary pathology was non-small cell lung cancer (44%), followed by breast cancer (19%), renal cell carcinoma (14%), melanoma (11%), and small cell lung cancer (5%). The median tumor volume and median largest diameter were 0.16 cm³ and 0.8 cm, respectively. In total, 1018 lesions (34%) were larger than 1 cm in maximum diameter. The PD for 2410 tumors (80%) was 24 Gy, for 408 tumors (13%) it was 19 to 23 Gy, and for 216 tumors (7%) it was 15 to 18 Gy. In total, 87 patients (10%) had local progression of 104 tumors (3%), and 148 patients (17%) had at least radiographic evidence of radiation necrosis involving 199 tumors (7%; 4% were symptomatic). Univariate and multivariate analyses were performed for local progression and radiation necrosis. For local progression, tumors less than 1 cm (subhazard ratio [SHR] 2.32; $p < 0.001$), PD of 24 Gy (SHR 1.84; $p = 0.01$), and additional whole-brain radiation therapy (SHR 2.53; $p = 0.001$) were independently associated with better outcome. For the development of radiographic radiation necrosis, independent prognostic factors included size greater than 1 cm (SHR 2.13; $p < 0.001$), location in the corpus callosum (SHR 5.72; $p < 0.001$), and uncommon pathologies (SHR 1.65; $p = 0.05$). Size (SHR 4.78; $p < 0.001$) and location (SHR 7.62; $p < 0.001$)-but not uncommon pathologies-were independent prognostic factors for the subgroup with symptomatic radiation necrosis. **CONCLUSIONS:** A PD of 24 Gy results in significantly better local control of metastases measuring < 2 cm than lower doses. In addition, tumor size is an independent prognostic factor for both local progression and radiation necrosis. Some tumor pathologies and locations may also contribute to an increased risk of radiation necrosis.

[186] More than Just the Number of Brain Metastases: Evaluating the Impact of Brain Metastasis Location and Relative Volume on Overall Survival After Stereotactic Radiosurgery.

World neurosurgery. 2017;99:111-117

Emery A, Trifiletti DM, Romano KD, Patel N, Smolkin ME, Sheehan JP
PMID: 27919761 DOI: 10.1016/j.wneu.2016.11.119

OBJECTIVE: Most evidence describing outcomes of patients with brain metastases is based on number of brain metastases, rather than location or volume. We evaluated the impact of tumor location and relative volume on overall survival (OS) among a large cohort of patients treated with stereotactic radiosurgery. **METHODS:** Clinical, radiographic, and dosimetric data were collected on patients treated with first (if multiple) stereotactic radiosurgery for brain metastases. Multivariate analyses were performed to investigate the impact of brain metastasis relative location and volume on OS after stereotactic radiosurgery. **RESULTS:** Analysis included 300 patients with 817 tumors (116 patients with single brain metastasis). The most common tumor locations were supratentorial (75% of tumors), cerebellar (19%), and brainstem (5%). Median tumor volume was 0.4 mL (range, 0.003-65.0 mL). Tumor-specific factors associated with inferior OS included brainstem location versus both supratentorial and

cerebellum locations for particular assumed values of cube root tumor volume ($P < 0.001$ for each) and increasing total supratentorial tumor volume ($P = 0.004$). Patients with supratentorial tumors and cerebellar tumors demonstrated similar OS, and cube root total tumor volume within the cerebellum and brainstem did not predict for OS. **CONCLUSIONS:** The presence of brainstem metastases and cumulative supratentorial tumor volume are adverse features that result in inferior survival. These results can be used to inform patient prognosis and future clinical trial design.

[187] Patients with Long-Term Control of Systemic Disease Are a Favorable Prognostic Group for Treatment of Brain Metastases with Stereotactic Radiosurgery Alone.

World neurosurgery. 2017;98:266-272

Ebner DK, Gorovets D, Rava P, Cielo D, Kinsella TJ, DiPetrillo TA, Hepel JT
PMID: 27838432 DOI: 10.1016/j.wneu.2016.11.010

BACKGROUND: Stereotactic radiosurgery (SRS) alone is an attractive option for treatment of brain metastases. SRS avoids whole-brain radiotherapy (WBRT)-associated morbidity, but is limited by regional central nervous system (CNS) failures and short survival in some patients. We evaluated a subgroup of patients with controlled systemic disease that could represent a favorable patient population for SRS alone. **METHODS:** All patients with brain metastases treated with SRS without WBRT at our institution between 2004 and 2014 were grouped into two cohorts: those with controlled systemic disease (CSD) for 1 year or longer before prior to presentation with brain metastases and those without (i.e., uncontrolled systemic disease [USD]). Rates of local and regional CNS failure, and overall survival were assessed with chi² and Student t tests. Cox regression analysis was performed to evaluate independent predictors of regional control and overall survival. **RESULTS:** Two hundred ninety-four patients underwent SRS to 697 lesions, of which 65 patients had CSD. Median follow-up was 9.7 months. There was no difference in local control between the two cohorts ($P = 0.795$). Regional CNS control was significantly better for patients with CSD (68% vs. 48%; $P = 0.001$). Overall survival at 1 and 5 years for CSD were 65% and 13% with USD yielding 41% and 7%, respectively ($P < 0.001$). Multivariate analysis demonstrated that USD (relative CSD) independently predicts regional failure (hazard ratio [HR], 1.75; $P = 0.008$) and shorter overall survival (HR, 1.55; $P = 0.007$). **CONCLUSIONS:** Patients with brain metastases after 1 year or longer of primary and systemic disease control represent a particularly favorable cohort, with lower regional CNS failure and prolonged survival, for an approach of SRS alone.

[188] Endoresection of large uveal melanomas: clinical results in a consecutive series of 200 cases.

The British journal of ophthalmology. 2017;101(2):204-208

Biewald E, Lautner H, Gok M, Horstmann GA, Sauerwein W, Fluhs D, Bornfeld N
PMID: 27121095 DOI: 10.1136/bjophthalmol-2015-307076

BACKGROUND: To report eye salvaging rate, visual acuity (VA), local recurrences, complications and the potential benefit of adjuvant brachytherapy after endoresection of large uveal melanomas. **METHODS:** 200 patients were included in this retrospective study. They were treated from March 1999 to December 2010 with preoperative stereotactic gamma knife radiosurgery followed by endoresection and adjuvant brachytherapy in most cases. **RESULTS:** A total of 200 patients were included in this study (113 male, 87 female). Mean tumour height was 9.4 mm and the largest basal diameter ranged from 6.3 to 20 mm. The median follow-up time was 32.3 months. In 13.4% the eye was retained with a VA of 20/50 or better, in 33.6% VA was ranging from 20/400 to 20/50 and 53% had a VA of less than 20/400. In almost 90% of the cases the eye was preserved at the final visit. In 15.5% additional major surgery was required. In terms of survival 15.5% of our patients developed liver metastases during follow-up and died. Local tumour recurrence was observed in 10 out of 200 patients (5%) and was mainly treated with enucleation. The use of an adjuvant ruthenium-106 plaque did not lower the recurrence or enucleation rate significantly. **CONCLUSIONS:** Eyes with a large uveal melanoma can be preserved by stereotactic radiotherapy followed

by endoresection with the chance to obtain useful vision in approximately half of the cases. Adjuvant brachytherapy has no beneficial effect except a reduction of the frequency for major revision surgery.

[189] Choosing a Prescription Isodose in Stereotactic Radiosurgery for Brain Metastases: Implications for Local Control.

World neurosurgery. 2017;98:761-767.e1

Romano KD, Trifiletti DM, Garda A, Xu Z, Schlesinger D, Watkins WT, Neal B, Lerner JM, Sheehan JP

PMID: 27867125 DOI: 10.1016/j.wneu.2016.11.038

OBJECTIVE: Stereotactic radiosurgery (SRS) achieves excellent local control (LC) with limited toxicity for most brain metastases. SRS dose prescription variables influence LC; therefore, we evaluated the impact of prescription isodose line (IDL) on LC after SRS. **METHODS:** A retrospective analysis of patients with brain metastases treated on a Gamma Knife platform from 2004 to 2014 was conducted. Clinical, toxicity, radiographic, and dosimetric data were collected. Cox proportional hazards regression was used to determine progression-free survival (PFS) and competing risks analysis was used to determine predictive factors for LC. **RESULTS:** A total of 134 patients with 374 brain metastases were identified with a median survival of 8.7 months (range, 0.2-64.8). The median tumor maximum dimension was 8 mm (range, 2-62 mm), median margin dose was 20 Gy (range, 5-24 Gy), and 12-month LC rate was 88.7%. On multivariate analysis, PFS improved with increasing IDL ($P = 0.003$) and decreased with non-small-cell lung cancer histology ($P = 0.001$). Margin dose, tumor size, conformality, and previous whole-brain irradiation failed to independently affect PFS. When adjusting for death as a competing risk, the cumulative likelihood of LC improved with higher IDL ($P = 0.04$). The rate of SRS-induced radiographic and clinical toxicity was low (16.6% and 1.5%, respectively), and neither was affected by IDL. **CONCLUSIONS:** Our results confirm that SRS for brain metastases results in favorable LC, particularly for patients with smaller tumors. We noted that dose delivery to a higher prescription IDL is associated with small but measurable improvements in LC. This finding could be related to higher dose just beyond the radiographically apparent tumor.

[190] Multisession gamma knife surgery for large brain metastases.

Journal of neuro-oncology. 2017;131(3):517-524

Hasegawa T, Kato T, Yamamoto T, Iizuka H, Nishikawa T, Ito H, Kato N

PMID: 27832430 DOI: 10.1007/s11060-016-2317-4

This study aimed to explore the safety and efficacy of multisession gamma knife surgery (GKS) for large brain metastases with a volume of 10 cm³ or larger. Fifty-six patients who had 65 brain metastases with a volume of at least 10 cm³ were treated with multisession GKS. Three-session GKS at a prescription dose of 10 Gy to the tumor margin per session with a 2-week interval between doses was performed in 3 patients. Other patients were treated with 2-session GKS at a prescription dose of 10-13 Gy to the tumor margin per session with an interval of 1-4 weeks. The median tumor volume was 21 cm³. The median survival was 7 months. The 6-, 12-, and 18-month survival rates were 62, 42, and 31%, respectively. The progression-free survival rates at 6, 12, and 18 months were 93, 80, and 74%, respectively. At the time of the first and last GKS sessions, the median tumor volumes were 21 and 15 cm³, respectively, which decreased to 5 cm³ with a median follow-up period of 6 months. Seventy-four percent of evaluated patients who had pre-GKS clinical symptoms obtained symptomatic improvement in a mean interval of 2 months. Multisession GKS was a safe and effective alternative to surgical resection for patients who had brain metastases with a tumor volume of 10 cm³ or larger. Although long-term results remain unclear, multisession GKS may be a suitable palliative treatment to preserve neurological function.

[191] The Influence of Biomarker Mutations and Systemic Treatment on Cerebral Metastases from NSCLC Treated with Radiosurgery.

Journal of Korean Neurosurgical Society. 2017;60(1):21-29

Lee MH, Kong DS, Seol HJ, Nam DH, Lee JI

PMID: 28061489 DOI: 10.3340/jkns.2016.0404.005

OBJECTIVE: The purpose of this study was to analyze outcomes and identify prognostic factors in patients with cerebral metastases from non-small cell lung cancer (NSCLC) treated with gamma knife radiosurgery (GKS) particularly, focusing on associations of biomarkers and systemic treatments. **METHODS:** We retrospectively reviewed the medical records of 134 patients who underwent GKS for brain metastases due to NSCLC between January 2002 and December 2012. Representative biomarkers including epidermal growth factor receptor (EGFR) mutation, K-ras mutation, and anaplastic lymphoma kinase (ALK) mutation status were investigated. **RESULTS:** The median overall survival after GKS was 22.0 months (95% confidence interval [CI], 8.8-35.1 months). During follow-up, 63 patients underwent salvage treatment after GKS. The median salvage treatment-free survival was 7.9 months (95% CI, 5.2-10.6 months). Multivariate analysis revealed that lower recursive partition analysis (RPA) class, small number of brain lesions, EGFR mutation (+), and ALK mutation (+) were independent positive prognostic factors associated with longer overall survival. Patients who received target agents 30 days after GKS experienced significant improvements in overall survival and salvage treatment-free survival than patients who never received target agents and patients who received target agents before GKS or within 30 days (median overall survival: 5.0 months vs. 18.2 months, and 48.0 months with p -value=0.026; median salvage treatment-free survival: 4.3 months vs. 6.1 months and 16.6 months with p -value=0.006, respectively). To assess the influence of target agents on the pattern of progression, cases that showed local recurrence and new lesion formation were analyzed according to target agents, but no significant effects were identified. **CONCLUSION:** The prognosis of patients with brain metastases of NSCLC after GKS significantly differed according to specific biomarkers (EGFR and ALK mutations). Our results show that target agents combined with GKS was related to significantly longer overall survival, and salvage treatment-free survival. However, target agents were not specifically associated with improved local control of the lesion treated by GKS either development of new lesions. Therefore, it seems that currently popular target agents do not affect brain lesions themselves, and can prolong survival by controlling systemic disease status.

2016

[192] Role of Gamma Knife(R) Radiosurgery for the Treatment of Brain Metastases from Gynecological Cancers.

Cureus. 2016;8(12):e947

Keller A, Ismail R, Potrebko PS, Pepe J, Wu M, Saigal K, Biagioli M, Shridhar R, Holloway R, Field M, Rao NG

PMID: 28168125 DOI: 10.7759/cureus.947

OBJECTIVE: Gamma Knife((R)) (GK) (Elekta Instruments, Stockholm, Sweden) radiosurgery is well established for treatment of brain metastases. There are limited data on patients treated with GK from gynecological cancers. The authors sought to determine the effectiveness of the GK in patients with brain metastases from gynecological cancers. **METHODS:** An IRB-approved database was queried for patients with gynecologic cancers treated with GK between June 1996 and May 2016. Imaging studies were reviewed post-SRS (stereotactic radiosurgery) to evaluate local control (LC) and distant brain control (DC). Overall survival (OS), local control, and distant brain control were calculated using the Kaplan-Meier (KM) method and log-rank test. **RESULTS:** Thirty-three patients underwent SRS for 73 separate cranial lesions. The median age was 58.5 years, and 17 (52%) also had extracranial metastases. Ten (30%) patients had previously received whole brain radiotherapy (WBRT), and 11 (33%) underwent concurrent WBRT. The median tumor volume was 0.96 cm³. Median radiographic follow-up was 11 months. At the time of treatment, 39% of patients were categorized as recursive

partitioning analysis (RPA) Class I, 55% as RPA Class II, and 6% as RPA Class III. The local failure rate was 8%. Five patients (15%) developed new brain lesions outside the radiation field with a median progression-free survival (PFS) of seven (range: 3-9) months. Median OS was 15 months from GK treatment. One-year OS was 72.9% from GK treatment. Primary cancer histology was a significant predictor of OS, favoring ovarian and endometrial cancer ($p = 0.03$). **CONCLUSIONS:** Gamma Knife stereotactic radiosurgery for gynecologic brain metastases leads to excellent control rates of treated lesions. Primary histology may have a significant impact on OS following GK, with improved survival seen with ovarian and cervical cancer following Gamma Knife radiosurgery ($p = 0.03$).

[193] Is upfront stereotactic radiosurgery a rational treatment option for very elderly patients with brain metastases? A retrospective analysis of 106 consecutive patients age 80 years and older.

BMC cancer. 2016;16(1):948

Yomo S, Hayashi M

PMID: 27978813 DOI: 10.1186/s12885-016-2983-9

BACKGROUND: Advanced age has been shown to be a factor predicting poor survival in patients with brain metastases (BM). There have been only a few studies focusing on stereotactic radiosurgery (SRS) for elderly BM patients. The present study aimed to investigate the efficacy and limitations of SRS for very elderly BM patients. **METHODS:** This was a retrospective observational study analyzing 106 consecutive patients (69 males/37 females) age 80 years and older who received upfront Gamma Knife SRS for BM between January 2009 and October 2015. The median age was 84 years, and the median Karnofsky performance status (KPS) was 70. Fifty-two patients had a solitary BM, and others multiple BM. The median cumulative tumor volume was 3.9 mL and the median dose prescribed was 20 Gy. Overall survival (OS), neurological death rates and distant and local intracranial tumor control rates were analyzed. **RESULTS:** No patients were lost to follow-up. Six-month and 12-month OS rates were 54% and 32%, respectively. The median OS time was 7.1 months. Competing risks analysis showed that 6-month and 12-month neurological death rates were 8% and 11%, respectively. In total, 245 / 311 tumors (79%) in 82 patients (77%) with sufficient radiological follow-up data were evaluated. Six-month and 12-month distant BM recurrence rates (per patient) after SRS were 17% and 25%, respectively. Six-month and 12-month rates of local tumor control (per lesion) were 94% and 89%, respectively. Repeat SRS, salvage WBRT and surgical resection were subsequently required in 25, 4 and 1 patient, respectively. Proportional hazard regression analysis showed that $KPS \geq 70$ (HR: 0.444, $P < .001$), controlled primary disease/no extracranial metastases (HR: 0.361, $P < .001$) and female sex (HR: 0.569, $P = 0.028$) were independent factors predicting better OS. Similarly, tumor volume (> 2 mL) was the only factor predicting a higher rate of local control failure (HR: 12.8, $P = 0.003$). **CONCLUSIONS:** The present study suggested an upfront SRS strategy to offer a feasible and effective treatment option for very elderly patients with limited BM. In the majority of patients, neurological death could be delayed or even prevented.

[194] Association Between Radiation Necrosis and Tumor Biology After Stereotactic Radiosurgery for Brain Metastasis.

International journal of radiation oncology, biology, physics. 2016;96(5):1060-1069

Miller JA, Bennett EE, Xiao R, Kotecha R, Chao ST, Vogelbaum MA, Barnett GH, Angelov L, Murphy ES, Yu JS, Ahluwalia MS, Suh JH, Mohammadi AM

PMID: 27742540 DOI: 10.1016/j.ijrobp.2016.08.039

BACKGROUND: The primary dose-limiting toxicity of stereotactic radiosurgery (SRS) is radiation necrosis (RN), which occurs after approximately 5% to 10% of treatments. This adverse event may worsen neurologic deficits, increase the frequency and cost of imaging, and necessitate prolonged treatment with steroids or antiangiogenic agents. Previous investigations have primarily identified lesion size and dosimetric constraints as risk factors for RN in small populations. We hypothesized that disease histology, receptor status, and mutational status are associated with RN. **METHODS AND MATERIALS:** All patients presenting with brain metastasis between 1997 and 2015 who underwent SRS and subsequent

radiographic follow-up at a single tertiary-care institution were eligible for inclusion. The primary outcome was the cumulative incidence of radiographic RN. Multivariate competing risks regression was used to identify biological risk factors for RN. **RESULTS:** 1939 patients (5747 lesions) were eligible for inclusion; 285 patients (15%) experienced radiographic RN after the treatment of 427 (7%) lesions. After SRS, the median time to RN was 7.6 months. After multivariate analysis, graded prognostic assessment, renal pathology, lesion diameter, and the heterogeneity index remained independently predictive of RN in the pooled cohort. In subset analyses of individual pathologies, HER2-amplified status (hazard ratio [HR] 2.05, $P = .02$), BRAF V600+ mutational status (HR 0.33, $P = .04$), lung adenocarcinoma histology (HR 1.89, $P = .04$), and ALK rearrangement (HR 6.36, $P < .01$) were also associated with RN. **CONCLUSIONS:** In the present investigation constituting the largest series of RN, several novel risk factors were identified, including renal histology, lung adenocarcinoma histology, HER2 amplification, and ALK/BRAF mutational status. These risk factors may be used to guide clinical trial design incorporating biological risk stratification or dose escalation. Future studies determining the optimal timing of targeted therapies are warranted to further define the risk of RN.

[195] Clinical outcomes in patients with brain metastases from breast cancer treated with single-session radiosurgery or whole brain radiotherapy.

Journal of neurosurgery. 2016;125(Suppl 1):26-30

Mix M, Elmarzouky R, O'Connor T, Plunkett R, Prasad D

PMID: 27903186 DOI: 10.3171/2016.7.GKS161541

OBJECTIVE: Gamma Knife radiosurgery (GKRS) is used to treat brain metastases from breast cancer (BMB) as the sole treatment or in conjunction with tumor resection and/or whole brain radiotherapy (WBRT). This study evaluates outcomes in BMB based on treatment techniques and tumor biological features. **METHODS:** The authors reviewed all patients treated with BMB between 2004 and 2014. Patients were identified from a prospectively collected radiosurgery database and institutional tumor registry; 214 patients were identified. Data were collected from aforementioned sources and supplemented with chart review where needed. Independent radiological review was performed for all available brain imaging in those treated with GKRS. Survival analyses are reported using Kaplan-Meier estimates. **RESULTS:** During the 10-year study period, 214 patients with BMB were treated; 23% underwent GKRS alone, 46% underwent a combination of GKRS and WBRT, and 31% underwent WBRT alone. Median survival after diagnosis of BMB in those treated with GKRS alone was 21 months, and in those who received WBRT alone it was 3 months. In those treated with GKRS plus WBRT, no significant difference in median survival was observed between those receiving WBRT upfront or in a salvage setting following GKRS (19 months vs 14 months, $p = 0.63$). The median survival of patients with total metastatic tumor volume of ≤ 7 cm³ versus > 7 cm³ was 20 months vs 7 months ($p < 0.001$). Human epidermal growth factor receptor-2 (Her-2) positively impacted survival after diagnosis of BMB (19 months vs 12 months, $p = 0.03$). Estrogen receptor status did not influence survival after diagnosis of BMB. No difference was observed in survival after diagnosis of BMB based on receptor status in those who received WBRT alone. **CONCLUSIONS:** In this single-institution series of BMB, the addition of WBRT to GKRS did not significantly influence survival, nor did the number of lesions treated with GKRS. Survival after the diagnosis of BMB was most strongly affected by Her-2 positivity and total metastatic tumor volume.

[196] Gamma Knife radiosurgery for brain metastases from pulmonary large cell neuroendocrine carcinoma: a Japanese multi-institutional cooperative study (JLGK1401).

Journal of neurosurgery. 2016;125(Suppl 1):11-17

Kawabe T, Yamamoto M, Sato Y, Yomo S, Kondoh T, Nagano O, Serizawa T, Tsugawa T, Okamoto H, Akabane A, Aita K, Sato M, Jokura H, Kawagishi J, Shuto T, Kawai H, Moriki A, Kenai H, Iwai Y, Gondo M, Hasegawa T, Yasuda S, Kikuchi Y, Nagatomo Y, Watanabe S, Hashimoto N

PMID: 27903179 DOI: 10.3171/2016.7.GKS161459

OBJECTIVE: In 1999, the World Health Organization categorized large cell neuroendocrine carcinoma (LCNEC) of the lung as a variant of large cell carcinoma, and LCNEC now accounts for 3% of all lung cancers. Although LCNEC is categorized among the non-small cell lung cancers, its biological behavior has recently been suggested to be very similar to that of a small cell pulmonary malignancy. The clinical outcome for patients with LCNEC is generally poor, and the optimal treatment for this malignancy has not yet been established. Little information is available regarding management of LCNEC patients with brain metastases (METs). This study aimed to evaluate the efficacy of Gamma Knife radiosurgery (GKRS) for patients with brain METs from LCNEC. **METHODS:** The Japanese Leksell Gamma Knife Society planned this retrospective study in which 21 Gamma Knife centers in Japan participated. Data from 101 patients were reviewed for this study. Most of the patients with LCNEC were men (80%), and the mean age was 67 years (range 39-84 years). Primary lung tumors were reported as well controlled in one-third of the patients. More than half of the patients had extracranial METs. Brain metastasis and lung cancer had been detected simultaneously in 25% of the patients. Before GKRS, brain METs had manifested with neurological symptoms in 37 patients. Additionally, prior to GKRS, resection was performed in 17 patients and radiation therapy in 10. A small cell lung carcinoma-based chemotherapy regimen was chosen for 48 patients. The median lesion number was 3 (range 1-33). The median cumulative tumor volume was 3.5 cm³, and the median radiation dose was 20.0 Gy. For statistical analysis, the standard Kaplan-Meier method was used to determine post-GKRS survival. Competing risk analysis was applied to estimate GKRS cumulative incidences of maintenance of neurological function and death, local recurrence, appearance of new lesions, and complications. **RESULTS:** The overall median survival time (MST) was 9.6 months. MSTs for patients classified according to the modified recursive partitioning analysis (RPA) system were 25.7, 11.0, and 5.9 months for Class 1+2a (20 patients), Class 2b (28), and Class 3 (46), respectively. At 12 months after GKRS, neurological death-free and deterioration-free survival rates were 93% and 87%, respectively. Follow-up imaging studies were available in 78 patients. The tumor control rate was 86% at 12 months after GKRS. **CONCLUSIONS:** The present study suggests that GKRS is an effective treatment for LCNEC patients with brain METs, particularly in terms of maintaining neurological status.

[197] Prognostic factors for melanoma brain metastases treated with stereotactic radiosurgery.

Journal of neurosurgery. 2016;125(Suppl 1):31-39

Bian SX, Routman D, Liu J, Yang D, Groshen S, Zada G, Trakul N, Wong MK, Yu C, Chang EL

PMID: 27903181 DOI: 10.3171/2016.8.GKS161359

OBJECTIVE: Stereotactic radiosurgery (SRS) is routinely used to treat brain metastases from melanoma due to their radioresistant nature. The median survival for these patients is 4-6 months, according to earlier studies. The aim of this study was to evaluate prognostic factors that influence survival in patients with metastatic melanoma to the brain treated with SRS. **METHODS:** This retrospective analysis included all patients with melanoma brain metastases treated with SRS at the University of Southern California between 1994 and 2015. For the entire cohort, the authors performed a multivariable Cox regression analysis with an end point of survival. Covariates included number of lesions, total intracranial tumor volume, age, sex, and treatment date prior to 2005 or 2005 onward. In the subset of patients with > 1 lesion, additional multivariable Cox regression was performed, with covariates of Karnofsky Performance Scale, Graded Prognostic Assessment, Recursive Partitioning Analysis, timing of metastases (synchronous/metachronous), change in lesion number, and previous whole-brain radiation therapy or resection in addition to the previously mentioned covariates. Overall survival (OS) was calculated from the day SRS was performed to the date of last follow-up or date of death. **RESULTS:** A total of 401 patients were available for analysis. The median follow-up was 35.1 months for patients alive at the time of analysis, and the median OS was 7.7 months for the entire cohort (95% CI 6.7-8.3 months). In the entire cohort, greater number of brain

lesions, higher total intracranial tumor volume, age > 50 years, treatment prior to 2005, and male sex were found to be statistically significant factors associated with worse survival. The strongest risk factors for decreased OS were tumor volume > 10 cm³ and ≥ 5 lesions, with hazard ratios for risk of death of 1.7 and 2.2, respectively. In the subset of patients with > 1 lesion, tumor volume > 10 cm³ and no resection were the only factors significantly associated with decreased OS, with hazard ratios of 1.9 and 2.0 (hazard ratio of 0.49 for resection), respectively. **CONCLUSIONS:** This study suggests that greater lesion number, higher intracranial tumor volume, older age, treatment prior to 2005, and male sex have prognostic significance for decreased OS in patients with melanoma brain metastases treated with SRS. Additionally, in the subset of patients with > 1 lesion, only higher total tumor volume and no resection were associated with worse survival.

[198] Follow-up results of brain metastasis patients undergoing repeat Gamma Knife radiosurgery.

Journal of neurosurgery. 2016;125(Suppl 1):2-10

Koiso T, Yamamoto M, Kawabe T, Watanabe S, Sato Y, Higuchi Y, Yamamoto T, Matsumura A, Kasuya H

PMID: 27903177 DOI: 10.3171/2016.6.GKS161404

OBJECTIVE: Stereotactic radiosurgery (SRS) without upfront whole-brain radiotherapy (WBRT) has influenced recent treatment recommendations for brain metastasis patients. However, in brain metastasis patients who undergo SRS alone, new brain metastases inevitably appear with relatively high incidences during post-SRS follow-up. However, little is known about the second SRS results. The treatment results of second SRS were retrospectively reviewed, mainly for newly developed or, uncommonly, for recurrent brain metastases in order to reappraise the efficacy of this treatment strategy with a special focus on the maintenance of neurological status and safety. **METHODS:** This was an institutional review board-approved, retrospective cohort study that used a prospectively accumulated database, including 3102 consecutive patients with brain metastases who underwent SRS between July 1998 and June 2015. Among these 3102 patients, 859 (376 female patients; median age 64 years; range 21-88 years) who underwent a second SRS without WBRT were studied with a focus on overall survival, neurological death, neurological deterioration, local recurrence, salvage SRS, and SRS-induced complications after the second SRS. Before the second SRS, the authors also investigated the clinical factors and radiosurgical parameters likely to influence these clinical outcomes. For the statistical analysis, the standard Kaplan-Meier method was used to determine post-second SRS survival and neurological death. A competing risk analysis was applied to estimate post-second SRS cumulative incidences of local recurrence, neurological deterioration, salvage SRS, and SRS-induced complications. **RESULTS:** The post-second SRS median survival time was 7.4 months (95% CI 7.0-8.2 months). The actuarial survival rates were 58.2% and 34.7% at 6 and 12 months after the second SRS, respectively. Among 789 deceased patients, the causes of death could not be determined in 24 patients, but were confirmed in the remaining 765 patients to be nonbrain diseases in 654 (85.5%) patients and brain diseases in 111 (14.5%) patients. The actuarial neurological death-free survival rates were 94.4% and 86.6% at 6 and 12 months following the second SRS. Multivariable analysis revealed female sex, Karnofsky Performance Scale score of 80% or greater, better modified recursive partitioning analysis class, smaller tumor numbers, and higher peripheral dose to be significant predictive factors for longer survival. The cumulative incidences of local recurrence were 11.2% and 14.9% at 12 and 24 months after the second SRS. The crude incidence of neurological deterioration was 7.1%, and the respective cumulative incidences were 4.5%, 5.8%, 6.7%, 7.2%, and 7.5% at 12, 24, 36, 48, and 60 months after the second SRS. SRS-induced complications occurred in 25 patients (2.9%) after a median post-second SRS period of 16.8 months (range 0.6-95.0 months; interquartile range 5.6-29.3 months). The cumulative incidences of complications were 1.4%, 2.0%, 2.4%, 3.0%, and 3.0% at 12, 24, 36, 48, and 60 months after the second SRS, respectively. **CONCLUSIONS:** Carefully selected patients with recurrent tumors-either new or locally recurrent-are favorable candidates for a second SRS, particularly in terms of neurological status maintenance and the safety of this treatment strategy.

[199] Microinvasive tumor endoresection in combination with ocular stereotactic radiosurgery.

Journal of neurosurgery. 2016;125(Suppl 1):58-63

Sinyavskiy OA, Troyanovsky RL, Ivanov PI, Golovin AS, Tibilov AV, Solonina SN, Astapenko AM, Zubatkina IS

PMID: 27903184 DOI: 10.3171/2016.7.GKS161550

OBJECTIVE: The use of Gamma Knife radiosurgery (GKRS) as monotherapy in the treatment of uveal melanoma (UM) allows clinicians to achieve high local tumor control with low recurrence but does not prevent secondary enucleation due to glaucoma in cases of large tumors. The authors analyzed indications for tumor endoresection (ER), the time interval between irradiation and surgery, and the features and results of performing ER for UM after GKRS. **METHODS:** Thirty-seven patients between 28 and 78 years of age (16 male and 11 female patients) with UM underwent GKRS with a dose of 70 to 80 Gy that was applied to the center of the tumor with complete immobilization of the eye during the procedure. Tumor resection with histological investigation was performed in 24 eyes (transscleral resection was performed in 3 eyes, and ER was performed in 21 eyes) at 3 to 97 days after GKRS, mainly during the first 2 or 3 weeks. As a rule, ER (21 eyes) was performed to treat large, centrally localized, or equatorial UMs with exudative macula-on retinal detachment that reduced vision. The average tumor height was 8.9 mm, and the average width was 13.7 mm at the base. ER for UM included phacoemulsification, microinvasive vitrectomy with transretinal tumor resection, laser photocoagulation, and application of a temporary silicone oil tamponade. Seven patients received intraocular injections of inhibitors of angiogenesis for the prevention and treatment of radiation neuroretinopathy. The follow-up period ranged from 8 to 41 months. **RESULTS:** Preservation of the eyes without tumor recurrence was achieved in all 37 patients after GKRS (monotherapy and combined therapy). One patient died of liver metastases at 21 months after GKRS. In the ER group (21 eyes), drug-resistant glaucoma with low visual acuity appeared in 4 eyes (19%) with long-existing total exudative retinal detachment and delayed operations. Severe radiation neuroretinopathy with macular edema occurred in 4 of 21 cases (19%). Intraocular injections of inhibitors of angiogenesis significantly decreased retinal edema. Residual rhegmatogenous retinal detachment was revealed in 1 eye (4.8%). The conservation of the patient's primary vision or its improvement were observed in 11 eyes (52.4%). Useful vision more than 0.1 was achieved in 12 cases (57%), and more than 0.3 was achieved in 8 cases (38%). **CONCLUSIONS:** As a result of this research, ER for UM after GKRS proved to be an effective method of combined eye-conserving treatment for large centrally localized or equatorial tumors at high risk of the emergence and development of toxic tumor syndrome. Perfect eye immobilization, timely ER, and multiple intraocular injections of inhibitors of angiogenesis saved not only the eye in all cases, but also useful vision in many cases. Close cooperation among radiosurgeons, ophthalmologists, and vitreoretinal surgeons is the key to effective treatment.

[200] A case-matched study of stereotactic radiosurgery for patients with brain metastases: comparing treatment results for those with versus without neurological symptoms.

Journal of neuro-oncology. 2016;130(3):581-590

Koiso T, Yamamoto M, Kawabe T, Watanabe S, Sato Y, Higuchi Y, Yamamoto T, Matsumura A, Kasuya H, Barfod BE

PMID: 27591775 DOI: 10.1007/s11060-016-2264-0

We aimed to reappraise whether post-stereotactic radiosurgery (SRS) results for brain metastases differ between patients with and without neurological symptoms. This was an institutional review board-approved, retrospective cohort study using our prospectively accumulated database including 2825 consecutive BM patients undergoing gamma knife SRS alone during the 15-year period since July 1998. The 2825 patients were divided into two groups: neurologically asymptomatic [group A, 1374 patients (48.6%)] and neurologically symptomatic [group B, 1451 (51.4%)]. Because there was considerable bias in pre-SRS clinical factors between groups A and B, a case-matched study was conducted. Ultimately, 1644 patients

(822 in each group) were selected. The standard Kaplan-Meier method was used to determine post-SRS survival. Competing risk analysis was applied to estimate cumulative incidences of neurological death, neurological deterioration, local recurrence, re-SRS for new lesions and SRS-induced complications. Post-SRS median survival times (MSTs) did not differ between the two groups; 7.8 months in group A versus 7.4 months in group B patients (HR 1.064, 95% CI 0.963-1.177, $p = 0.22$). However, cumulative incidences of neurological death (HR 1.637, 95% CI 1.174-2.281, $p = 0.0036$) and neurological deterioration (HR 1.425, 95% CI 1.073-1.894, $p = 0.014$) were significantly lower in the group A than in the group B patients. Neurologically asymptomatic patients undergoing SRS for BM had better results than symptomatic patients in terms of both maintenance of good neurological state and prolonged neurological survival. Thus, we conclude that screening computed tomography/magnetic resonance imaging is highly beneficial for managing cancer patients.

[201] Factors influencing local tumor control after Gamma Knife radiosurgery for intracranial metastases from breast cancer.

Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2016;33:154-158

Suzuki S, Inoue T, Ishido K

PMID: 27452133 DOI: 10.1016/j.jocn.2016.03.037

Because evaluation of Gamma Knife radiosurgery (GKRS) for brain metastases (METs) has mainly been based on overall or progression-free survival rates, that is, patients' general condition and control of the primary disease, we focused on factors influencing local tumor control after GKRS for METs from breast cancer. Data were retrospectively collected from our institution's records of patients who had undergone GKRS twice or more for METs from breast cancer. Failed GKRS was defined as a tumor needing re-treatment by further GKRS or having already been treated by other modalities prior to later GKRS procedures. Influences of various factors on local tumor control were examined. GKRS was performed on 623 tumors in 123 sessions in 90 patients. Median follow up was 9 months (range 1-41 months). According to multivariate analysis, use of HER2-targeting agents, (hazard ratio [HR] 0.42, 95% confidence interval [CI] 0.18-0.99, $p = 0.049$), five or more lesions (HR 0.24, 95% CI 0.11-0.51, $p < 0.001$), volume $> 1.2\text{cm}^3$ (HR 3.12, 95% CI 1.62-6.02, $p < 0.001$), use of GK model B (HR 2.53, 95% CI 1.28-4.98, $p = 0.0076$), and prescribed dosage 18Gy (HR 0.19, 95% CI 0.01-0.51, $p < 0.001$) were predictors of failed GKRS. Patients with METs from breast cancer with HER2-positive tumors, five or more lesions, and tumors of volume 1.2cm^3 are good candidates for GKRS. GK model C and Perfexion achieve better local tumor control than does GK model B. The recommended dosage is 18Gy.

[202] Management approach for recurrent brain metastases following upfront radiosurgery may affect risk of subsequent radiation necrosis.

Advances in radiation oncology. 2016;1(4):294-299

Rae A, Gorovets D, Rava P, Ebner D, Cielo D, Kinsella TJ, DiPetrillo TA, Hepel JT
PMID: 28740900 DOI: 10.1016/j.adro.2016.08.007

PURPOSE: Many patients treated with stereotactic radiosurgery (SRS) alone as initial treatment require 1 or more subsequent salvage therapies. This study aimed to determine if commonly used salvage strategies are associated with differing risks of radiation necrosis (RN). **METHODS AND MATERIALS:** All patients treated with upfront SRS alone for brain metastases at our institution were retrospectively analyzed. Salvage treatment details were obtained for brain failures. Patients who underwent repeat SRS to the same lesion were excluded. RN was determined based on pathological confirmation or advanced brain imaging consistent with RN in a symptomatic patient. Patients were grouped according to salvage treatment and rates of RN were compared via Fisher's exact tests. **RESULTS:** Of 284 patients treated with upfront SRS alone, 132 received salvage therapy and 44 received multiple salvage treatments. This included 31 repeat SRS alone, 58 whole brain radiation therapy (WBRT) alone, 28 SRS and WBRT, 7 surgery alone, and 8 surgery with adjuvant radiation. With a median follow-up of 10 months, the rate of RN among all patients was 3.17% (9/284), salvaged patients 4.55% (6/132), and never

salvaged patients 1.97% (3/152). Receiving salvage therapy did not significantly increase RN risk ($P = .31$). Of the patients requiring salvage treatments, the highest RN rate was among patients that had both salvage SRS and WBRT (delivered as separate salvage therapies) (6/28, 21.42%). RN rate in this group was significantly higher than in those treated with repeat SRS alone (0/31), WBRT alone (0/58), surgery alone (0/7), and surgery with adjuvant radiation (0/8). Comparing salvage WBRT doses <30 Gy versus ≥ 30 Gy revealed no effect of dose on RN rate. Additionally, among patients who received multiple SRS treatments, number of treated lesions was not predictive of RN incidence. **CONCLUSION:** Our results suggest that initial management approach for recurrent brain metastasis after upfront SRS does not affect the rate of RN. However, the risk of RN significantly increases when patients are treated with both repeat SRS and salvage WBRT. Methods to improve prediction of toxicity and optimize patient selection for salvage treatments are needed.

[203] Neurological Change after Gamma Knife Radiosurgery for Brain Metastases Involving the Motor Cortex.

Brain tumor research and treatment. 2016;4(2):111-115

Park CY, Choi HY, Lee SR, Roh TH, Seo MR, Kim SH

PMID: 27867921 DOI: 10.14791/btrt.2016.4.2.111

BACKGROUND: Although Gamma Knife radiosurgery (GKRS) can provide beneficial therapeutic effects for patients with brain metastases, lesions involving the eloquent areas carry a higher risk of neurologic deterioration after treatment, compared to those located in the non-eloquent areas. We aimed to investigate neurological change of the patients with brain metastases involving the motor cortex (MC) and the relevant factors related to neurological deterioration after GKRS. **METHODS:** We retrospectively reviewed clinical, radiological and dosimetry data of 51 patients who underwent GKRS for 60 brain metastases involving the MC. Prior to GKRS, motor deficits existed in 26 patients (50.9%). The mean target volume was 3.2 cc (range 0.001-14.1) at the time of GKRS, and the mean prescription dose was 18.6 Gy (range 12-24 Gy). **RESULTS:** The actuarial median survival time from GKRS was 19.2 \pm 5.0 months. The calculated local tumor control rates at 6 and 12 months after GKRS were 89.7% and 77.4%, respectively. During the median clinical follow-up duration of 12.3 \pm 2.6 months (range 1-54 months), 18 patients (35.3%) experienced new or worsened neurologic deficits with a median onset time of 2.5 \pm 0.5 months (range 0.3-9.7 months) after GKRS. Among various factors, prescription dose (>20 Gy) was a significant factor for the new or worsened neurologic deficits in univariate ($p=0.027$) and multivariate ($p=0.034$) analysis. The managements of 18 patients were steroid medication ($n=10$), boost radiation therapy ($n=5$), and surgery ($n=3$), and neurological improvement was achieved in 9 (50.0%). **CONCLUSION:** In our series, prescription dose (>20 Gy) was significantly related to neurological deterioration after GKRS for brain metastases involving the MC. Therefore, we suggest that careful dose adjustment would be required for lesions involving the MC to avoid neurological deterioration requiring additional treatment in the patients with limited life expectancy.

[204] Timing and type of immune checkpoint therapy affect the early radiographic response of melanoma brain metastases to stereotactic radiosurgery.

Cancer. 2016;122(19):3051-8

Qian JM, Yu JB, Kluger HM, Chiang VL

PMID: 27285122 DOI: 10.1002/cncr.30138

BACKGROUND: Growing evidence suggests that immunotherapy and radiation therapy can be synergistic in the treatment of cancer. This study was performed to determine the effect of the relative timing and type of immune checkpoint therapy on the response of melanoma brain metastases (BrMets) to treatment with stereotactic radiosurgery (SRS). **METHODS:** Seventy-five melanoma patients with 566 BrMets were treated with both SRS and immune checkpoint therapy between 2007 and 2015 at a single institution. Immunotherapy and radiosurgery treatment of any single lesion were considered concurrent if SRS was administered within 4

weeks of immunotherapy. The impact of the timing and type of immunotherapy on the lesional response was determined with the Wilcoxon rank-sum test, which was used to compare the median percent lesion volume change 1.5, 3, and 6 months after SRS treatment, with significance determined by $P = .0167$ according to the Bonferroni correction for multiple comparisons. **RESULTS:** Concurrent use of immunotherapy and SRS resulted in a significantly greater median percent reduction in the lesion volume at 1.5 (-63.1% vs -43.2%, $P < .0001$), 3 (-83.0% vs -52.8%, $P < .0001$), and 6 months (-94.9% vs -66.2%, $P < .0001$) in comparison with nonconcurrent therapy. The median percent reduction in the lesion volume was also significantly greater for anti-programmed cell death protein 1 (anti-PD-1) than anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) at 1.5 (-71.1% vs -48.2%, $P < .0001$), 3 (-89.3% vs -66.2%, $P < .0001$), and 6 months (-95.1% vs -75.9%, $P = .0004$). **CONCLUSIONS:** The administration of immunotherapy within 4 weeks of SRS results in an improved lesional response of melanoma BrMets in comparison with treatment separated by longer than 4 weeks. Anti-PD-1 therapy also results in a greater lesional response than anti-CTLA-4 after SRS. *Cancer* 2016;122:3051-3058. (c) 2016 American Cancer Society.

[205] Palliative Resection of Metastatic Brain Tumors Previously Treated by Stereotactic Radiosurgery.

Brain tumor research and treatment. 2016;4(2):116-123

Jeon YS, Koh YC, Song SW, Cho J, Lim SD

PMID: 27867922 DOI: 10.14791/btrt.2016.4.2.116

BACKGROUND: Therapeutic approaches to brain metastases include surgery, whole-brain radiotherapy, stereotactic radiosurgery (SRS), and combination therapy. Recently, postoperative or preoperative SRS draws more attention to reduce postoperative recurrence in brain metastases. The goal of this study is to review surgical outcome of patients who had been treated by SRS, and to discuss the effectiveness of preoperative SRS. **METHODS:** From 2009 to 2015, 174 patients were treated by SRS for brain metastases, and among these 50 patients underwent surgery. Eighteen patients underwent surgery after SRS, and 14 had oligometastases. The patients' median age at the time of surgery was 56 years (range, 34-84 years). The median follow-up duration was 16.5 months (range, 4-47 months). Pathological findings were classified as follows; radiation necrosis (Group I, $n=3$), mixed type (Group II, $n=2$), and tumor-dominant group (Group III, $n=9$). We compared surgical outcome in respect of steroid, mannitol dosage, Karnofsky performance scale, and pathological subgroups. **RESULTS:** The median overall survival was 11 months (range, 2-40 months). Six, 12 and 24 months survival rate was 64.3, 42.9, and 28.6%, respectively. Improvement of Karnofsky performance score was achieved in 50% after surgery. The overall survival of Group I (26.6 months) was longer than the other groups (11.5 months). Additionally the patients were able to be weaned from medications, such as steroid administration after surgery was reduced in 10 cases, and mannitol dosage was reduced in 6 cases. Time interval within 3 months between SRS and surgery seemed to be related with better local control. **CONCLUSION:** Surgical resection after radiologically and symptomatically progressed brain metastases previously treated with SRS seems to be effective in rapid symptom relief and provides an improvement in the quality of life. A short time interval between SRS and surgical resection seems to be associated with good local tumor control.

[206] Optimal Treatment Decision for Brain Metastases of Unknown Primary Origin: The Role and Timing of Radiosurgery.

Brain tumor research and treatment. 2016;4(2):107-110

Han HJ, Chang WS, Jung HH, Park YG, Kim HY, Chang JH

PMID: 27867920 DOI: 10.14791/btrt.2016.4.2.107

BACKGROUND: Up to 15% of all patients with brain metastases have no clearly detected primary site despite intensive evaluation, and this incidence has decreased with the use of improved imaging technology. Radiosurgery has been evaluated as one of the treatment modality for patients with limited brain metastases. In this study, we evaluated the effectiveness of radiosurgery for brain metastases from unknown primary tumors. **METHODS:** We retrospectively

evaluated 540 patients who underwent gamma knife radiosurgery (GKRS) for brain metastases radiologically diagnosed between August 1992 and September 2007 in our institution. First, the brain metastases were grouped into metachronous, synchronous, and precocious presentations according to the timing of diagnosis of the brain metastases. Then, synchronous and precocious brain metastases were further grouped into 1) unknown primary; 2) delayed known primary; and 3) synchronous metastases according to the timing of diagnosis of the primary origin. We analyzed the survival time and time to new brain metastasis in each group. **RESULTS:** Of the 540 patients, 29 (5.4%) presented precocious or synchronous metastases (34 GKRS procedures for 174 lesions). The primary tumor was not found even after intensive and repeated systemic evaluation in 10 patients (unknown primary, 34.5%); found after 8 months in 3 patients (delayed known primary, 1.2%); and diagnosed at the same time as the brain metastases in 16 patients (synchronous metastasis, 55.2%). No statistically significant differences in survival time and time to new brain metastasis were found among the three groups. **CONCLUSION:** Identification of a primary tumor before GKRS did not affect the patient outcomes. If other possible differential diagnoses were completely excluded, early GKRS can be an effective treatment option for brain metastases from unknown primary tumor.

[207] Evaluation of Dose-Staged Gamma Knife Radiosurgical Treatment Method for High-Risk Brain Metastases.

World neurosurgery. 2016;94:352-359

Frischer JM, Fraller A, Mallouhi A, Vogl UM, Baier F, Ertl A, Preusser M, Knosp E, Kitz K, Gatterbauer B

PMID: 27443227 DOI: 10.1016/j.wneu.2016.07.038

OBJECTIVES: The study aim was to evaluate the utility of 2-fraction, dose-staged Gamma Knife radiosurgery (GKRS) in patients with large, high-risk brain metastases (BMs). **METHODS:** A total of 63 large BMs in eloquent areas in 61 patients were treated with GKRS in 2 reduced doses. Treatment planning was conducted on the 50% isodose line and included the whole tumor volume as seen on T1 contrast-enhanced and T2-weighted magnetic resonance imaging sections. The median margin and central dose were 12 Gy and 24 Gy, respectively, for both fractions. Patients were assessed using the Graded Prognostic Assessment, Recursive Partitioning Analysis, and Score Index for Radiosurgery. **RESULTS:** Thirty-two patients (53%) had been diagnosed with multiple BMs, and extracranial metastases were present in a majority of patients before GKRS treatment. Significant decreases in tumor volume were observed between the first and second treatment stages. At 3-month follow-up, a majority of patients presented with stable or decreased lesion volumes. The remaining patients showed intralesional hemorrhaging or increasing edema that was managed conservatively. Three patients were diagnosed with tumor progression at the last follow-up and received microsurgical treatment. The median time to radiologic progression was 7 months. The median survival time after initial BM diagnosis was 6 months. Survival times were significantly longer than 3 of 4 calculated prognostic survival estimates. **CONCLUSION:** The new 2-fraction, dose-staged GKRS concept seems to be a well-tolerated and effective treatment option for large BMs. This method may be indicated in elderly patients or patients with surgical contraindications with large or high-risk brain metastases.

[208] The Effect of Gene Alterations and Tyrosine Kinase Inhibition on Survival and Cause of Death in Patients With Adenocarcinoma of the Lung and Brain Metastases.

International journal of radiation oncology, biology, physics. 2016;96(2):406-413

Sperduto PW, Yang TJ, Beal K, Pan H, Brown PD, Bangdiwala A, Shanley R, Yeh N, Gaspar LE, Braunstein S, Sneed P, Boyle J, Kirkpatrick JP, Mak KS, Shih HA, Engelman A, Roberge D, Arvold ND, Alexander B, Awad MM, Contessa J, Chiang V, Hardie J, Ma D, Lou E, Sperduto W, Mehta MP

PMID: 27598807 DOI: 10.1016/j.ijrobp.2016.06.006

PURPOSE: Lung cancer remains the most common cause of both cancer mortality and brain metastases (BM). The purpose of this study was to assess the effect of

gene alterations and tyrosine kinase inhibition (TKI) on median survival (MS) and cause of death (CoD) in patients with BM from lung adenocarcinoma (L-Adeno).

METHODS: A multi-institutional retrospective database of patients with L-Adeno and newly diagnosed BM between 2006 and 2014 was created. Demographics, gene alterations, treatment, MS, and CoD were analyzed. The treatment patterns and outcomes were compared with those in prior trials. **RESULTS:** Of 1521 L-Adeno patients, 816 (54%) had known alteration status. The gene alteration rates were 29%, 10%, and 26% for EGFR, ALK, and KRAS, respectively. The time from primary diagnosis to BM for EGFR+/+ was 10/15 months (P=.02) and for ALK-/+ was 10/20 months (P<.01), respectively. The MS for the group overall (n=1521) was 15 months. The MS from first treatment for BM for EGFR and ALK-, EGFR+, ALK+ were 14, 23 (P<.01), and 45 (P<.0001) months, respectively. The MS after BM for EGFR+ patients who did/did not receive TKI before BM was 17/30 months (P<.01), respectively, but the risk of death was not statistically different between TKI-naive patients who did/did not receive TKI after the diagnosis of BM (EGFR/ALK hazard ratios: 1.06 [P=.84]/1.60 [P=.45], respectively). The CoD was nonneurologic in 82% of patients with known CoD. **CONCLUSION:** EGFR and ALK gene alterations are associated with delayed onset of BM and longer MS relative to patients without these alterations. The CoD was overwhelmingly nonneurologic in patients with known CoD.

[209] Stereotactic Radiosurgery for Brainstem Metastases: An International Cooperative Study to Define Response and Toxicity.

International journal of radiation oncology, biology, physics. 2016;96(2):280-288

Trifiletti DM, Lee CC, Kano H, Cohen J, Janopaul-Naylor J, Alonso-Basanta M, Lee JYK, Simonova G, Liscak R, Wolf A, Kvint S, Grills IS, Johnson M, Liu KD, Lin CJ, Mathieu D, Heroux F, Silva D, Sharma M, Cifarelli CP, Watson CN, Hack JD, Golfinos JG, Kondziolka D, Barnett G, Lunsford LD, Sheehan JP

PMID: 27478166 DOI: 10.1016/j.ijrobp.2016.06.009

PURPOSE: To pool data across multiple institutions internationally and report on the cumulative experience of brainstem stereotactic radiosurgery (SRS).

METHODS AND MATERIALS: Data on patients with brainstem metastases treated with SRS were collected through the International Gamma Knife Research Foundation. Clinical, radiographic, and dosimetric characteristics were compared for factors prognostic for local control (LC) and overall survival (OS) using univariate and multivariate analyses. **RESULTS:** Of 547 patients with 596 brainstem metastases treated with SRS, treatment of 7.4% of tumors resulted in severe SRS-induced toxicity (grade \geq 3, increased odds with increasing tumor volume, margin dose, and whole-brain irradiation). Local control at 12 months after SRS was 81.8% and was improved with increasing margin dose and maximum dose. Overall survival at 12 months after SRS was 32.7% and impacted by age, gender, number of metastases, tumor histology, and performance score. **CONCLUSIONS:** Our study provides additional evidence that SRS has become an option for patients with brainstem metastases, with an excellent benefit-to-risk ratio in the hands of experienced clinicians. Prior whole-brain irradiation increases the risk of severe toxicity in brainstem metastasis patients undergoing SRS.

[210] A cure is possible: a study of 10-year survivors of brain metastases.

Journal of neuro-oncology. 2016;129(3):545-555

Kotecha R, Vogel S, Suh JH, Barnett GH, Murphy ES, Reddy CA, Parsons M, Vogelbaum MA, Angelov L, Mohammadi AM, Stevens GHJ, Peereboom DM, Ahluwalia MS, Chao ST

PMID: 27456950 DOI: 10.1007/s11060-016-2208-8

Little is known on the natural history, recurrence patterns, neurocognitive outcomes and prognostic factors associated with survival in long-term survivors (\geq 10 years) from brain metastasis (BM). In this study, the records of 1953 patients who underwent treatment for BM with a potential for \geq 10 years of follow-up were reviewed. Cox regression analysis identified factors predictive for overall survival (OS). The median age at brain metastasis diagnosis was 60 years and the median OS was 6.4 months. The 1-year OS rate was 29.9, 12.1 % at 2 years, 3.0 % at 5 years, and 1.3 % at 10 years. On multivariable analysis, factors associated with worse OS included gender (males,

HR 1.2), multiple brain metastases (HR 1.3), no surgery (HR 1.8), and no stereotactic radiosurgery (HR 1.8) ($p < 0.0001$ each). Fifty-six patients (2.9%) survived ≥ 5 years; 23 patients (1.2%) survived ≥ 10 years and the median survival for ≥ 10 year survivors was 18.5 years. Six of the 10-year survivors had an intracranial recurrence, five occurred within 11 years from the first treatment. Presence of a solitary lesion or single lesion at the time of brain metastasis diagnosis was associated with improved survival. Eight of the ≥ 10 year survivors (34.8%) had no neurological symptoms at last follow-up; none of the 10-year survivors were documented to have a neurologic death. Our study demonstrates that patients with favorable prognostic features should undergo multimodality treatment. Albeit rare, patients who are alive 10 years after treatment for their brain metastases may be considered cured from their intracranial disease.

[211] Analysis of the benefit of sequential cranial radiotherapy in patients with EGFR mutant non-small cell lung cancer and brain metastasis.

Medical oncology (Northwood, London, England). 2016;33(8):97
Byeon S, Ham JS, Sun JM, Lee SH, Ahn JS, Park K, Ahn MJ
PMID: 27447711 DOI: 10.1007/s12032-016-0811-3

Although cranial radiotherapy is considered the standard treatment for brain metastasis (BM), EGFR tyrosine kinase inhibitors (TKIs) have shown promising activity in EGFR mutant non-small cell lung cancer (NSCLC) patients with BM. However, the efficacy of sequential cranial radiotherapy in patients with EGFR mutant NSCLC who are treated with EGFR TKIs remains to be determined. Patients with NSCLC who harbored an EGFR mutation and whose BM had been treated with EGFR TKIs were retrospectively reviewed. The clinical outcomes of patients treated with EGFR TKIs alone and those treated with cranial radiotherapy followed by EGFR TKIs (additive therapy) were compared. Of the 573 patients with NSCLC with BM who harbored an EGFR mutation and had received EGFR TKIs, 121 (21.1%) had BM at the time of initial diagnosis. Fifty-nine (49%) patients were treated with additive therapy, whereas 62 (51%) patients were treated only with EGFR TKIs. No significant differences were observed between the additive therapy group and the EGFR TKI alone group regarding intracranial progression-free survival (PFS) (16.6 vs 21.0 months, $p = 0.492$) or extracranial PFS (12.9 vs 15.0 months, $p = 0.770$). The 3-year survival rates were similar in both groups (71.9 vs 68.2%, $p = 0.675$). Additive therapy consisting of cranial radiotherapy followed by EGFR TKI treatment did not improve OS or intracranial PFS compared with EGFR TKI treatment alone in EGFR mutant NSCLC patients with BM. Further prospective studies are needed to determine the precise benefits of sequential cranial radiotherapy in EGFR mutant NSCLC treated with EGFR TKIs.

[212] Cumulative Intracranial Tumor Volume (CITV) Enhances the Prognostic Value of the Lung-Specific Graded Prognostic Assessment (GPA) Model.

Neurosurgery. 2016;79(2):246-52
Marcus LP, Marshall D, Hirshman BR, McCutcheon BA, Gonda DD, Koiso T, Hattangadi-Gluth JA, Carter BS, Yamamoto M, Chen CC
PMID: 26579964 DOI: 10.1227/NEU.0000000000001123

BACKGROUND: Management of patients afflicted with brain metastasis requires tailoring of therapeutic strategies based on survival expectations. Therefore, the development of prognostic indices is of critical importance in this patient population. **OBJECTIVE:** To determine whether the cumulative intracranial tumor volume (CITV) of brain metastasis augments the prognostic value of the lung-specific Graded Prognostic Assessment (GPA) index. **METHODS:** Patient data were derived from 365 lung cancer patients with brain metastasis who were consecutively treated with stereotactic radiosurgery at the University of California, San Diego/San Diego Gamma Knife Center. CITV was analyzed to determine the volume cutoff that maximized sensitivity and specificity for 1-year survival. Multivariate Cox proportional hazard modeling was performed, and overall survival was estimated by the Kaplan-Meier method risk stratifying with or without this optimal CITV. The prognostic value of these models (lung-specific GPA +/- CITV) was quantitatively compared with the use of net reclassification improvement (>0) and integrated discrimination improvement. **RESULTS:** For the University of California, San Diego/San Diego Gamma Knife Center

cohort, the CITV cutoff that had the greatest survival discrimination at 1 year was 4 cm. The addition of CITV to the lung-specific GPA indexes significantly improved the prognostic value of lung-specific GPA, with net reclassification improvement >0 of 0.430 (95% confidence interval, 0.228-0.629) and integrated discrimination improvement of 0.029 (95% confidence interval, 0.004-0.073). These findings were validated in an independent cohort of 1638 lung cancer patients with brain metastasis who were treated with stereotactic radiosurgery at the Katsuta Hospital Mito Gamma House in Japan. **CONCLUSION:** In independent cohorts, the addition of CITV to the lung-specific GPA index significantly improved the prognostic value of this index. **ABBREVIATIONS:** AUC, area under the receiver-operating characteristic curve; BM, brain metastasis; CITV, cumulative intracranial tumor volume; med-GPA, disease-specific Graded Prognostic Assessment; GPA, Graded Prognostic Assessment; IDI, integrated discrimination improvement; KHMGH, Katsuta Hospital Mito Gamma House; KPS, Karnofsky Performance Status; NRI, net reclassification improvement; ROC, receiver-operating characteristic curve; SRS, stereotactic radiosurgery; UCSD/SDGKC, University of California, San Diego/San Diego Gamma Knife Center.

[213] Does Modern Management of Malignant Extracranial Disease Prolong Survival in Patients with ≥ 3 Brain Metastases?

World neurosurgery. 2016;92:279-283
Karlsson B, Yamamoto M, Hanssens P, Beute G, Kawabe T, Koiso T, Soderman M, Lim K, Rosen CL, Yeo TT
PMID: 27154179 DOI: 10.1016/j.wneu.2016.04.089

OBJECTIVE: To assess if modern management of extracranial malignant diseases has prolonged the survival times for patients with more than 2 brain metastases (BM). **METHODS:** Data from 2385 patients treated with Gamma Knife surgery (GKS) for ≥ 3 BM between 1982 and 2011 were retrospectively analyzed. The patients were divided into 6 groups based on the treatment year and the median and 10% survival times were compared with the median and mean treatment dates in each group. **RESULTS:** The later the treatment date, the longer the median as well as the 10% survival times. The relation between the median treatment date and both the 10% and median survival times could be accurately expressed by a linear as well as an exponential curve fit. The median and 10% survival times increased by around 80% and 150%, respectively, between 1990 and 2010. **CONCLUSIONS:** Both the median and 10% survival times have increased in recent years among patients with more than 2 BM treated with GKS. Both linear and exponential regressions accurately expressed the increase in both median and 10% survival times during the years 1990-2010. Findings from other published data support the observation of longer survival times among patients treated more recently, independent of the patients being treated with GKS or with whole-brain radiation therapy with or without radiosurgery. Thus, earlier findings of short survival times for patients with multiple BM are no longer valid, at least not for patients deemed suitable for radiosurgery. Aggressive management is thus warranted for these patients.

[214] Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases: A Randomized Clinical Trial.

JAMA. 2016;316(4):401-409
Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK, Carrero XW, Barker FG 2nd, Deming R, Burri SH, Menard C, Chung C, Stieber VW, Pollock BE, Galanis E, Buckner JC, Asher AL
PMID: 27458945 DOI: 10.1001/jama.2016.9839

IMPORTANCE: Whole brain radiotherapy (WBRT) significantly improves tumor control in the brain after stereotactic radiosurgery (SRS), yet because of its association with cognitive decline, its role in the treatment of patients with brain metastases remains controversial. **OBJECTIVE:** To determine whether there is less cognitive deterioration at 3 months after SRS alone vs SRS plus WBRT. **DESIGN, SETTING, AND PARTICIPANTS:** At 34 institutions in North America, patients with 1 to 3 brain metastases were randomized to receive SRS or SRS plus WBRT

between February 2002 and December 2013. **INTERVENTIONS:** The WBRT dose schedule was 30 Gy in 12 fractions; the SRS dose was 18 to 22 Gy in the SRS plus WBRT group and 20 to 24 Gy for SRS alone. **MAIN OUTCOMES AND MEASURES:** The primary end point was cognitive deterioration (decline >1 SD from baseline on at least 1 cognitive test at 3 months) in participants who completed the baseline and 3-month assessments. Secondary end points included time to intracranial failure, quality of life, functional independence, long-term cognitive status, and overall survival. **RESULTS:** There were 213 randomized participants (SRS alone, n = 111; SRS plus WBRT, n = 102) with a mean age of 60.6 years (SD, 10.5 years); 103 (48%) were women. There was less cognitive deterioration at 3 months after SRS alone (40/63 patients [63.5%]) than when combined with WBRT (44/48 patients [91.7%]; difference, -28.2%; 90% CI, -41.9% to -14.4%; P < .001). Quality of life was higher at 3 months with SRS alone, including overall quality of life (mean change from baseline, -0.1 vs -12.0 points; mean difference, 11.9; 95% CI, 4.8-19.0 points; P = .001). Time to intracranial failure was significantly shorter for SRS alone compared with SRS plus WBRT (hazard ratio, 3.6; 95% CI, 2.2-5.9; P < .001). There was no significant difference in functional independence at 3 months between the treatment groups (mean change from baseline, -1.5 points for SRS alone vs -4.2 points for SRS plus WBRT; mean difference, 2.7 points; 95% CI, -2.0 to 7.4 points; P = .26). Median overall survival was 10.4 months for SRS alone and 7.4 months for SRS plus WBRT (hazard ratio, 1.02; 95% CI, 0.75-1.38; P = .92). For long-term survivors, the incidence of cognitive deterioration was less after SRS alone at 3 months (5/11 [45.5%] vs 16/17 [94.1%]; difference, -48.7%; 95% CI, -87.6% to -9.7%; P = .007) and at 12 months (6/10 [60%] vs 17/18 [94.4%]; difference, -34.4%; 95% CI, -74.4% to 5.5%; P = .04). **CONCLUSIONS AND RELEVANCE:** Among patients with 1 to 3 brain metastases, the use of SRS alone, compared with SRS combined with WBRT, resulted in less cognitive deterioration at 3 months. In the absence of a difference in overall survival, these findings suggest that for patients with 1 to 3 brain metastases amenable to radiosurgery, SRS alone may be a preferred strategy. **TRIAL REGISTRATION:** clinicaltrials.gov Identifier: NCT00377156.

[215] Gamma Knife radiosurgery combined with stereotactic aspiration as an effective treatment method for large cystic brain metastases.

Oncology letters. 2016;12(1):343-347
Wang H, Qi S, Dou C, Ju H, He Z, Ma Q
PMID: 27347148 DOI: 10.3892/ol.2016.4603

In the present study, the efficacy and clinical outcomes of stereotactic aspiration combined with the Gamma Knife radiosurgery (GKRS) method were evaluated retrospectively for patients with large cystic brain metastases. This combined method aims to decrease the tumor weight (volume) and increase the possible radiation dose. The present study involved 48 patients who were diagnosed with cystic metastatic brain tumors between January 2008 and December 2012 in the Department of Neurosurgery of Nanfang Hospital Southern Medical University (Guangzhou, China). Every patient underwent Leksell stereotactic frame, 1.5T magnetic resonance imaging (MRI)-guided stereotactic cyst aspiration and Leksell GKRS. Subsequent to the therapy, MRI was performed every 3 months. The results indicated that 48 cases were followed up for 24-72 months, with a mean follow-up duration of 36.2 months. Following treatment, 44 patients (91.7%) exhibited tumor control and 4 patients (8.3%) experienced progression of the local tumor. During this period, 35 patients (72.9%) succumbed, but only 2 (4.2%) of these succumbed to the brain metastases. The total local control rate was 91.7% and the median overall survival time of all patients was 19.5 months. The 1-year overall survival rate was 70.8% and the 2-year overall survival rate was 26.2%. **In conclusion,** these results indicated that the method of stereotactic cyst aspiration combined with GKRS was safe and effective for patients with large cystic brain metastases. This method is effective for patients whose condition is too weak for general anesthesia and in whom the tumors are positioned at eloquent areas. This method enables patients to avoid a craniotomy, and provides a good tumor control rate, survival time and quality of life.

[216] Does immunotherapy increase the rate of radiation necrosis after radiosurgical treatment of brain metastases?

Journal of neurosurgery. 2016;125(1):17-23
Colaco RJ, Martin P, Kluger HM, Yu JB, Chiang VL
PMID: 26544782 DOI: 10.3171/2015.6.JNS142763
OBJECT Radiation necrosis (RN), or its imaging equivalent, treatment-related imaging changes (TRIC), is an inflammatory reaction to high-dose radiation in the brain. The authors sought to investigate the hypothesis that immunotherapy increases the risk of developing RN/TRIC after stereotactic Gamma Knife (GK) radiosurgery for brain metastases. **METHODS:** A total of 180 patients who underwent GK surgery for brain metastases between 2006 and 2012 were studied. The systemic therapy they received was classified as cytotoxic chemotherapy (CT), targeted therapy (TT), or immunotherapy (IT). The timing of systemic therapy in relation to GK treatment was also recorded. Logistic regression was used to calculate the odds of developing RN according to type of systemic therapy received. **RESULTS:** The median follow-up time was 11.7 months. Of 180 patients, 39 (21.7%) developed RN/TRIC. RN/TRIC rates were 37.5% (12 of 32) in patients who received IT alone, 16.9% (14 of 83) in those who received CT only, and 25.0% (5 of 20) in those who received TT only. Median overall survival was significantly longer in patients who developed RN/TRIC (23.7 vs 9.9 months, respectively). The RN/TRIC rate was increased significantly in patients who received IT alone (OR 2.40 [95% CI 1.06-5.44]; p = 0.03), whereas receipt of any CT was associated with a lower risk of RN/TRIC (OR 0.38 [95% CI 0.18-0.78]; p = 0.01). The timing of development of RN/TRIC was not different between patients who received IT and those who received CT. **CONCLUSIONS:** Patients who receive IT alone may have an increased rate of RN/TRIC compared with those who receive CT or TT alone after stereotactic radiosurgery, whereas receiving any CT may in fact be protective against RN/TRIC. As the use of immunotherapies increases, the rate of RN/TRIC may be expected to increase compared with rates in the chemotherapy era.

[217] Stereotactic Radiosurgery for Poor Performance Status Patients.

International journal of radiation oncology, biology, physics. 2016;95(3):956-959
Kubicek GJ, Turtz A, Xue J, Patel A, Richards G, LaCouture T, Cappelli L, Diestelkamp T, Saraiya P, Bexon A, Lerman N, Goldman HW
PMID: 27113565 DOI: 10.1016/j.ijrobp.2016.02.041

PURPOSE: Patients with poor performance status (PS), usually defined as a Karnofsky Performance Status of 60 or less, were not eligible for randomized stereotactic radiosurgery (SRS) studies, and many guidelines suggest that whole-brain radiation therapy (WBRT) is the most appropriate treatment for poor PS patients. **METHODS AND MATERIALS:** In this retrospective review of our SRS database, we identified 36 patients with PS of 60 or less treated with SRS for central nervous system (CNS) metastatic disease. PS, as defined by the Karnofsky Performance Status, was 60 (27 patients), 50 (8 patients), or 40 (1 patient). The median number of CNS lesions treated was 3. **RESULTS:** Median overall survival (OS) was 7.2 months (range, 0.73-25.6 months). Fifteen patients (41%) were alive at 6 months, and 6 patients (16.6%) were alive at 1 year. There was no difference in OS in patients who underwent previous WBRT. There were no local failures or cases of radiation toxicity. Distant CNS failures were seen in 9 patients (25%). **CONCLUSIONS:** Our patients with poor PS had reasonable median OS and relatively low distant CNS failure rates. Patients in this patient population may be ideal candidates for SRS compared with WBRT given the low incidence of distant failure over their remaining lives and the favorable logistics of single-fraction treatment for these patients with debility and their caregivers.

[218] Pretreatment clinical prognostic factors for brain metastases from breast cancer treated with Gamma Knife radiosurgery.

Surgical neurology international. 2016;7(Suppl 35):S830-S836
Roehrig AT, Ferrel EA, Benincosa DA, MacKay AR, Ling BC, Carlson JD, Demakas JJ, Wagner A, Lamoreaux WT, Fairbanks RK, Call JA, Cooke BS, Peressini B, Lee CM
PMID: 27990315 DOI: 10.4103/2152-7806.194065

BACKGROUND: Brain metastases significantly affect morbidity and mortality rates for patients with metastatic breast cancer. Treatment for brain metastases lengthens survival, and options such as stereotactic radiosurgery (SRS) can increase survival to 12 months or longer. This study retrospectively analyzes the prognostic factors for overall survival (OS) for patients with one or multiple brain metastases from breast cancer treated with SRS. **METHODS:** Between December 2001 and May 2015, 111 patients with brain metastases from breast cancer were grouped by potential prognostic factors including age at diagnosis, Karnofsky Performance Status (KPS) score, number of brain metastases, and whether or not they received adjuvant treatments such as whole brain radiotherapy (WBRT) or surgical resection. Survival rates were determined for all groups, and hazard ratios were calculated using univariate and multivariate analyses to compare differences in OS. **RESULTS:** Median OS was 16.8 +/- 4.22 months. Univariate analysis of patients with a KPS ≤ 60 and multivariate analysis of KPS 70-80 showed significantly shorter survival than those with KPS 90-100 (5.9 +/- 1.22 months, 21.3 +/- 11.69 months, and 22.00 +/- 12.56 months, $P = 0.024$ and < 0.001). Other results such as age ≥ 65 years and higher number of brain metastases trended toward shorter survival but were not statistically significant. No difference in survival was found for patients who had received WBRT in addition to SRS ($P = 0.779$). **CONCLUSION:** SRS has been shown to be safe and effective in treating brain metastases from breast cancer. We found our median survival to be 16.8 +/- 4.22 months, an increase from other clinical reports. In addition, 38.4% of our population was alive at 2 years and 15.6% survived 5 years. Significant prognostic factors can help inform clinical treatment decisions. This study found that KPS was a significant prognostic indicator of OS in these patients.

[219] Demonstration of differential radiosensitivity based upon mutation profile in metastatic melanoma treated with stereotactic radiosurgery.

Journal of radiosurgery and SBRT. 2016;4(2):97-106
Rutter CE, Johung KL, Yao X, Lu AY, Jilaveanu LB, Yu JB, Contessa JN, Kluger HM, Chiang VLS, Bindra RS
PMID: 29296434 DOI:

BACKGROUND: Metastatic melanoma often involves the brain. Radiotherapy is an important treatment of melanoma brain metastases, although melanoma radiosensitivity is considered heterogeneous. Thus, identifying subsets with differential radiosensitivity is essential. **MATERIALS AND METHODS:** Patients with metastatic melanoma were identified in a prospective stereotactic radiosurgery (SRS) database. Tumor were tested for alterations in B-RAF, N-RAS, and c-KIT. Standardized imaging following SRS was reviewed for recurrence. Differences in local and distant failure were determined using modified Cox proportional hazards models. **RESULTS:** 102 patients and 1,028 brain metastases were included. N-RAS mutated patients were significantly less likely to develop local recurrence after SRS than wild type patients (HR 0.17, 95% CI 0.04-0.72, $p=0.017$). B-RAF and c-KIT mutations were not associated with altered rates of local recurrence. Lower local recurrence rates for N-RAS mutated tumors persisted on multivariate analysis (HR 0.18, 95% CI 0.04-0.84 $p=0.029$). **CONCLUSIONS:** N-RAS mutation is associated with improved local control following SRS. Local recurrence is more common in wild type patients and those with B-RAF or c-KIT mutations. Further research is needed to validate these findings and integrate into practice.

[220] Gamma Knife radiosurgery for cystic brain metastases.

British journal of neurosurgery. 2016;30(1):43-8
Lee SR, Oh JY, Kim SH
PMID: 25958957 DOI: 10.3109/02688697.2015.1039489

OBJECTIVE: The goal of this study was to investigate the treatment results of Gamma Knife radiosurgery (GKRS) for cystic brain metastases and relevant factors associated with local tumor control. **MATERIALS AND METHODS:** We retrospectively reviewed the clinical, radiological, and dosimetry data of 37 cystic brain metastases of 28 patients who were treated with GKRS. Cyst drainage was performed in 8 large lesions before GKRS to decrease the target volume.

The mean target volume was 4.8 (range, 0.3-15.8) cc at the time of GKRS, and the mean prescription dose was 16.6 (range, 13-22) Gy. **RESULTS:** The actuarial median survival time was 17.7 +/- 10.2 months, and the primary tumor status was a significant prognostic factor for survival. The actuarial local tumor control rate at 6 and 12 months was 93.1 and 82.3%, respectively. Among the various factors, only prescription dose (>15 Gy) was a significant factor related to local tumor control after multivariate analysis ($p = 0.049$). Cyst volume or cyst/total tumor volume ratio did not influence local control after GKRS, when the target volume was reduced to about 15 cc after cyst drainage. **CONCLUSION:** According to our results, we suggest that stereotactic radiosurgery should be considered as one of the treatment options for cystic brain metastases, when large tumor volume can be reduced by surgical drainage before radiosurgery, especially for patients with a controlled primary tumor.

[221] BRAF Mutation Is Associated with Improved Local Control of Melanoma Brain Metastases Treated with Gamma Knife Radiosurgery.

Frontiers in oncology. 2016;6:107
Gallaher IS, Watanabe Y, DeFor TE, Dusenbery KE, Lee CK, Hunt MA, Lin HY, Yuan J
PMID: 27200295 DOI: 10.3389/fonc.2016.00107

OBJECTIVES: Evidence has implicated a possible role of tumor mutation status on local control (LC) with radiotherapy. BRAF is a proto-oncogene that is mutated in approximately 50% of patients with melanoma. We sought to analyze the influence of BRAF status on LC of melanoma brain metastases (MBM) following Gamma Knife radiosurgery (GK). **METHODS:** Among 125 patients treated with GK for MBM at our institution between 2006 and 2015, we identified 19 patients with 69 evaluable metastases whose BRAF mutation status was known and follow-up imaging was available. LC of individual metastases was compared based on BRAF mutation status using statistical techniques to control for measurements of multiple metastases within each patient. CNS progression was defined as either local failure or development of new lesions. **RESULTS:** Of the 69 metastases, BRAF was mutated in 30 and wild-type in 39. With a median follow-up of 30 months for all patients and a median follow-up of 5.5 months for treated lesions, 1-year LC was significantly better among metastases with mutated vs. wild-type BRAF (69 vs. 34%, RR = 0.3, 95% CI = 0.1-0.7, $p = 0.01$). BRAF mutation was found to be a significant predictor of LC after stereotactic radiosurgery (SRS) in both univariate [RR = 0.3 (95% CI 0.1-0.7, $p = 0.01$)] and multivariate [RR = 0.2 (95% CI 0.1-0.7, $p = 0.01$)] analyses. There was also a trend toward improved CNS progression free survival (PFS) at 1 year (26 vs. 0%, $p = 0.06$), favoring BRAF-mutated patients. **CONCLUSION:** In this retrospective study, MBM treated with GK had significantly improved LC for patients with BRAF mutation vs. wild-type. Our data suggest that BRAF mutation may sensitize tumors to radiosurgery, and that BRAF wild-type tumors may be more radioresistant.

[222] Fractionated Stereotactic Gamma Knife Radiosurgery for Large Brain Metastases: A Retrospective, Single Center Study.

PloS one. 2016;11(9):e0163304
Kim JW, Park HR, Lee JM, Kim JW, Chung HT, Kim DG, Jung HW, Paek SH
PMID: 27661613 DOI: 10.1371/journal.pone.0163304

PURPOSE: Stereotactic radiosurgery (SRS) is widely used for brain metastases but has been relatively contraindicated for large lesions (>3 cm). In the present study, we analyzed the efficacy and toxicity of hypofractionated Gamma Knife radiosurgery to treat metastatic brain tumors for which surgical resection were not considered as the primary treatment option. **METHODS AND MATERIALS:** Thirty-six patients, forty cases were treated with Gamma Knife-based fractionated SRS for three to four consecutive days with the same Leksell frame on their heads. The mean gross tumor volume was 18.3 cm³(3), and the median dose was 8 Gy at 50% isodose line with 3 fractions for three consecutive days (range, 5 to 11 Gy and 2 to 4 fractions for 2 to 4 consecutive days). Survival rates and prognostic factors were analyzed. **RESULTS:** The overall survival rate at one and two years was 66.7 and 33.1%, respectively. The median survival time was 16.2 months, and

the local control rate was 90%. RTOG toxicity grade 1 was observed in 3 (8.3%) patients, grade 2 in 1 (2.7%) patient and grade 3 in 1 (2.7%) patient respectively. Radiation necrosis was developed in 1 (2.7%) patient. KPS scores and control of primary disease resulted in significant differences in survival. **CONCLUSIONS:** Our findings suggest that consecutive hypofractionated Gamma Knife SRS could be applied to large metastatic brain tumors with effective tumor control and low toxicity rates.

[223] Predicting treatment related imaging changes (TRICs) after radiosurgery for brain metastases using treatment dose and conformity metrics.

Journal of radiosurgery and SBRT. 2016;4(1):53-60

Taylor BF, Knisely JP, Qian JM, Yu JB, Chiang VL

PMID: 29296426 DOI:

PURPOSE: Treatment-related imaging changes (TRICs) after stereotactic radiosurgery (SRS) involves the benign transient enlargement of radiographic lesions after treatment. Identifying the radiation dose volumes and conformity metrics associated with TRICs for different post-treatment periods would be helpful and improve clinical decision making. **METHODS:** 367 metastases in 113 patients were treated using Gamma Knife SRS between 1/1/2007-12/31/2009. Each metastasis was measured at each imaging follow-up to detect TRICs (defined as $\geq 20\%$ increase in volume). Fluctuations in small volume lesions (less than 108 mm³) were ignored given widely variable conformity indices (CI) for small volumes. The Karolinska Adverse Radiation Effect (KARE) factor, Paddick's CI, Shaw's CI, tumor volume (TV), 10 Gy (V10) and 12 Gy (V12) volumes, and prescription isodose volume (PIV) were calculated. **RESULTS:** From 0-6 months, all measures correlated with the incidence of TRICs ($p < .001$), except KARE, which was inversely correlated. During the 6-12 month period all measures except KARE were still correlated. Beyond 12 months, no correlation was found between any of the measures and the development of TRICs. **CONCLUSIONS:** All metrics except KARE were associated with TRICs from 0-12 months only. Additional patient and treatment factors may become dominant at greater times after SRS.

[224] Local control of brain metastases after stereotactic radiosurgery: the impact of whole brain radiotherapy and treatment paradigm.

Journal of radiosurgery and SBRT. 2016;4(2):89-96

Hughes RT, Black PJ, Page BR, Lucas JT Jr, Qasem SA, Watabe K, Ruiz J, Laxton AW, Tatter SB, Debinski W, Chan MD

PMID: 29296433 DOI:

PURPOSE: We investigate clinical, pathologic, and treatment paradigm-related factors affecting local control of brain metastases after stereotactic radiosurgery (SRS) with or without whole brain radiotherapy (WBRT). **METHODS AND MATERIALS:** Patients with brain metastases treated with SRS alone, before or after WBRT were considered to determine predictors of local failure (LF), time to failure and survival. **RESULTS:** Among 137 patients, 411 brain metastases were analyzed. 23% of patients received SRS alone, 51% received WBRT prior to SRS, and 26% received SRS followed by WBRT. LF occurred in 125 metastases: 63% after SRS alone, 20% after WBRT then SRS, and 22% after SRS then WBRT. Median time to local failure was significantly less after SRS alone compared to WBRT then SRS (12.1 v. 22.7 months, $p = 0.003$). Tumor volume was significantly associated with LF (HR:5.2, $p < 0.001$, 95% CI:3.4-7.8). **CONCLUSIONS:** WBRT+SRS results in reduced LF. Local control was not significantly different after SRS as salvage therapy versus upfront SRS.

[225] A contemporary dose selection algorithm for stereotactic radiosurgery in the treatment of brain metastases - An initial report.

Journal of radiosurgery and SBRT. 2016;4(1):43-52

Colaco RJ, Yu JB, Bond JS, Bindra RS, Contessa JN, Knisely JPS, Chiang VL

PMID: 29296425 DOI:

Summary: Indications and treatment goals for SRS have changed since the publication of RTOG 90-05. We present initial retrospective outcomes from a new dose selection algorithm in use at our institution felt to be more contemporary

with doses being used in the radiosurgery community today and report our local control and toxicity outcomes. This dose selection algorithm will be subject to a forthcoming prospective phase 2 trial. **INTRODUCTION:** To evaluate safety and efficacy of an institutional dose selection algorithm in the treatment of brain metastases (BM) with single fraction radio-surgery (SRS). **METHODS AND MATERIALS:** The medical records of 65 patients with ≤ 10 BM treated with GK at our institution between April 2012 and October 2012 were reviewed retrospectively. The prescription doses used in this study ranged from 16-22Gy and were based upon RTOG 90-05 guideline doses subsequently modified at our institution depending on lesion number, lesion volume, institutional experience and prior history of whole brain radiation therapy (WBRT). Primary endpoint was local recurrence (LR) with additional outcomes measured including distant intracranial recurrence (DIR), death without local recurrence (DWLR) and alive and disease free (ADF). Fine Gray competing risk analysis was used to examine factors affecting local recurrence. **RESULTS:** Median follow up was 8.9 months (range 1.0-29.6months) and 12 month overall survival was 37% (95% CI 24.9-49.1%). Overall local recurrence rate was 7.7%. On competing risks regression analysis, no variable was significantly associated with local recurrence, including previous whole brain radiotherapy (WBRT), (SHR 1.21 [95%CI 0.13-11.5], $p = 0.87$ and radioresistant versus radiosensitive histology (SHR 0.51 [95% CI 0.06-7.73], $p = 0.55$). No patient developed grade 3 or higher neurotoxicity at 12 months following GK. **CONCLUSIONS:** Initial local control and toxicity results from our institutional dose selection algorithm are reported here. Comparison of our results with RTOG 90-05 is difficult due to significant differences in the patient population and their treatments. The applicability of this algorithm merits further investigation across multiple centers for the purpose of treatment and clinical trial standardization in single fraction SRS and will be the subject of a forthcoming phase 2 prospective study within our own institution.

[226] Kidney cancer with brain metastases. Prognostic factors and treatment outcome.

Voprosy onkologii. 2016;62(4):442-9

Golanov AV, Banov SM, Vetlova ER, Dreval ON, Bekyashev AK, Iliylov SR, Antipina NA, Durgaryan AA, Pogosova AA

PMID: 30475528 DOI:

The aim of this study was to study the effectiveness of stereotactic radiosurgery by Gamma Knife in kidney cancer with brain metastases. There were analyzed results in 112 patients with such spread of the disease who received treatment in the Gamma Knife Center, Moscow. The median age of patients was 58 years (range, 33-77 years). Total number of metastatic lesions was 444, and the average number of brain metastases in one patient 4 (from 1 to 30). A single brain metastasis had 28 patients (25%). Median of total volume of brain metastasis for each patient was 5.9 cm³ (from 0.1 to 29,1sm³). Mean marginal dose for metastatic lesion was 22 Gy (from 12 Gy to 26 Gy) and the average value of isodose, on which planning was performed - 64% (from 39% to 99%). The overall survival after radiosurgery was 37,7%, 16,4% and 9,3% for 12, 24 and 36 months, respectively, with a median overall survival of 9,1 months (95% CI = 7,1-11,8). New brain metastases after radiosurgical treatment occurred in 44 (54,3%) patients with a median of 10,1 months. (95% CI = 7-18). Local recurrences after radiosurgical treatment were detected in 19 (17%) patients with a median of 6,6 months (95% CI = 4,0-9,6). The Karnovsky index was > 80 . Local control was achieved in 96% of metastatic lesions in 87% of patients. Side effects of radiosurgical treatment occurred in 33.8% of patients (6% radionecrosis and 23.8% an increase of perifocal edema). Thus stereotactic radiosurgery by Gamma Knife is an effective treatment option for brain metastases in kidney cancer providing a high level of local control of metastatic lesions with minimal neurotoxicity. In a case of distant recurrence reuse of such treatment provides good local control and improves overall survival compared with other methods of treatment.

[227] Impact of Deferring Radiation Therapy in Patients With Epidermal Growth Factor Receptor-Mutant Non-Small Cell Lung Cancer Who Develop Brain Metastases.

International journal of radiation oncology, biology, physics. 2016;95(2):673-9
Magnuson WJ, Yeung JT, Guillod PD, Gettinger SN, Yu JB, Chiang VL
PMID: 27034176 DOI: 10.1016/j.ijrobp.2016.01.037

PURPOSE: To perform a retrospective analysis of patients with epidermal growth factor receptor (EGFR)-mutant lung adenocarcinoma who developed brain metastases (BM) to evaluate our hypothesis that the use of upfront EGFR-tyrosine kinase inhibitors (TKIs), and deferral of radiation therapy (RT), would result in inferior intracranial progression-free survival but similar overall survival (OS).

METHODS AND MATERIALS: Of 202 patients diagnosed with EGFR-mutant NSCLC between July 1, 2008, and December 31, 2014, 71 developed BM. Twenty-one patients were excluded owing to prior EGFR-TKI use, EGFR-TKI resistance mutation, failure to receive EGFR-TKI after whole-brain radiation therapy (WBRT)/stereotactic radiosurgery (SRS) or <6 months' follow-up. Of the remaining 50 patients, 17 received upfront EGFR-TKI followed by SRS or WBRT, 17 WBRT then EGFR-TKI, and 16 SRS followed by EGFR-TKI. Disease-specific-graded prognostic assessment was similar among all 3 groups. **RESULTS:** The median OS was longer in the upfront RT group compared with the upfront EGFR-TKI group (34.1 vs 19.4 months; $P=.01$). On subgroup analysis, the SRS group had longer OS than the upfront EGFR-TKI group (58.4 vs 19.4 months; $P=.01$), but the WBRT group did not (29.9 vs 19.4 months; $P=.09$). Intracranial progression-free survival was improved in patients receiving upfront RT compared with those receiving upfront EGFR-TKI (37.9 vs 10.6 months; $P<.001$). **CONCLUSIONS:** The present study suggests that the use of upfront EGFR-TKI, and the deferral of SRS or WBRT, may result in inferior OS in patients with EGFR-mutant NSCLC who develop brain metastases. A prospective, multi-institutional, randomized trial of upfront EGFR-TKI with RT at intracranial progression versus upfront RT followed by EGFR-TKI is urgently needed.

[228] Gamma Knife Surgery for Metastatic Brain Tumors from Gynecologic Cancer.

World neurosurgery. 2016;89:455-63
Matsunaga S, Shuto T, Sato M
PMID: 26844877 DOI: 10.1016/j.wneu.2016.01.062

OBJECTIVE: The incidences of metastatic brain tumors from gynecologic cancer have increased. The results of Gamma Knife surgery (GKS) for the treatment of patients with brain metastases from gynecologic cancer (ovarian, endometrial, and uterine cervical cancers) were retrospectively analyzed to identify the efficacy and prognostic factors for local tumor control and survival. **METHODS:** The medical records were retrospectively reviewed of 70 patients with 306 tumors who underwent GKS for brain metastases from gynecologic cancer between January 1995 and December 2013 in our institution. **RESULTS:** The primary cancers were ovarian in 33 patients with 147 tumors and uterine in 37 patients with 159 tumors. Median tumor volume was 0.3 cm³. Median marginal prescription dose was 20 Gy. The local tumor control rates were 96.4% at 6 months and 89.9% at 1 year. There was no statistically significant difference between ovarian and uterine cancers. Higher prescription dose and smaller tumor volume were significantly correlated with local tumor control. Median overall survival time was 8 months. Primary ovarian cancer, controlled extracranial metastases, and solitary brain metastasis were significantly correlated with satisfactory overall survival. Median activities of daily living (ADL) preservation survival time was 8 months. Primary ovarian cancer, controlled extracranial metastases, and higher Karnofsky Performance Status score were significantly correlated with better ADL preservation. **CONCLUSIONS:** GKS is effective for control of tumor progression in patients with brain metastases from gynecologic cancer, and may provide neurologic benefits and preservation of the quality of life.

[229] Management patterns of patients with cerebral metastases who underwent multiple stereotactic radiosurgeries.

Journal of neuro-oncology. 2016;128(1):119-128
Marshall DC, Marcus LP, Kim TE, McCutcheon BA, Goetsch SJ, Koiso T, Alksne JF, Ott K, Carter BS, Hattangadi-Gluth JA, Yamamoto M, Chen CC
PMID: 26948673 DOI: 10.1007/s11060-016-2084-2

With escalating focus on cost containment, there is increasing scrutiny on the practice of multiple stereotactic radiosurgeries (SRSs) for patients with cerebral metastases distant to the initial tumor site. Our goal was to determine the survival patterns of patients with cerebral metastasis who underwent multiple SRSs. We retrospectively analyzed survival outcomes of 801 patients with 3683 cerebral metastases from primary breast, colorectal, lung, melanoma and renal histologies consecutively treated at the University of California, San Diego/San Diego Gamma Knife Center (UCSD/SDGKC), comparing the survival pattern of patients who underwent a single ($n = 643$) versus multiple SRS(s) ($n = 158$) for subsequent cerebral metastases. Findings were recapitulated in an independent cohort of 2472 patients, with 26,629 brain metastases treated with SRS at the Katsuta Hospital Mito GammaHouse (KHMGGH). For the UCSD/SDGKC cohort, no significant difference in median survival was found for patients undergoing 1, 2, 3, or ≥ 4 SRS(s) (median survival of 167, 202, 129, and 127 days, respectively). Median intervals between treatments consistently ranged 140-178 days irrespective of the number of SRS(s) (interquartile range 60-300; $p = 0.25$). Patients who underwent >1 SRSs tend to be younger, with systemic disease control, harbor lower cumulative tumor volume but increased number of metastases, and have primary melanoma ($p < 0.001$, <0.001 , <0.001 , 0.02, and 0.009, respectively). Comparable results were found in the KHMGGH cohort. Using an independent validation study design, we demonstrated comparable overall survival between judiciously selected patients who underwent a single or multiple SRS(s).

[230] How Does Brainstem Involvement Affect Prognosis in Patients with Limited Brain Metastases? Results of a Matched-Cohort Analysis.

World neurosurgery. 2016;88:563-568
Trifiletti DM, Lee CC, Shah N, Patel NV, Chen SC, Sheehan JP
PMID: 26555507 DOI: 10.1016/j.wneu.2015.10.089

OBJECTIVE: Although brainstem metastases are thought to portend an inferior prognosis compared to non-brainstem brain metastases, there is limited evidence to support this claim, particularly in the modern radiosurgical era. **METHODS:** We collected the clinical data for 500 patients with brain metastases treated at our institution with stereotactic radiosurgery (SRS). All patients received SRS to at least one brain metastasis, and all brainstem metastases underwent SRS. After propensity score matching, clinical characteristics and overall survival were calculated and compared between groups. **RESULTS:** Three hundred sixteen patients with brain metastases were analyzed after matching (143 with brainstem involvement and 173 without). Patients with brainstem metastases lived shorter after first SRS than patients without brainstem metastases did (median 4.4 and 6.5 months, respectively; $P = 0.01$), and they were more likely to have received whole brain irradiation ($P = 0.003$). Patients with a single metastasis did not survive longer than patients with multiple brain metastases if there was brainstem involvement ($P = 0.45$). The incidence of new extracranial disease and severe toxicity after SRS did not differ between groups. **CONCLUSIONS:** The survival of patients with brain metastases is inferior after a metastatic lesion develops within the brainstem, despite favorable local control with brainstem SRS. The brainstem location should be considered a negative prognostic factor for survival after SRS, and it could result from the eloquence of this location. Future research could identify the clinically life-limiting component of brainstem metastases.

[231] Retrospective Study of Metastatic Melanoma and Renal Cell Carcinoma to the Brain with Multivariate Analysis of Prognostic Pre-Treatment Clinical Factors.

International journal of molecular sciences. 2016;17(3):400
Ferrel EA, Roehrig AT, Kaya EA, Carlson JD, Ling BC, Wagner A, MacKay AR, Call JA, Demakas JJ, Lamoreaux WT, Fairbanks RK, Cooke BS, Peressini B, Lee CM

PMID: 26999120 DOI: 10.3390/ijms17030400

Patients with brain metastasis from renal cell carcinoma (RCC) or melanoma have historically had very poor prognoses of less than one year. Stereotactic radiosurgery (SRS) can be an effective treatment for patients with these tumors. This study analyzes the effect of pretreatment prognostic factors on overall survival (OS) for RCC and melanoma patients with metastasis to the brain treated with SRS. A total of 122 patients with brain metastases from either RCC or melanoma were grouped by age at brain metastasis diagnosis, whether they received whole brain radiation therapy (WBRT) in addition to SRS, or they underwent surgical resection, Karnofsky Performance Score (KPS), number of brain metastases, and primary tumor. Median survival times for melanoma patients and RCC patients were 8.20 +/- 3.06 and 12.70 +/- 2.63 months, respectively. Patients with >5 metastases had a significantly shorter median survival time (6.60 +/- 2.45 months) than the reference group (1 metastasis, 10.70 +/- 13.40 months, $p = 0.024$). Patients with KPS ≤ 60 experienced significantly shorter survival than the reference group (KPS = 90-100), with median survival times of 5.80 +/- 2.46 months ($p < 0.001$) and 45.20 +/- 43.52 months, respectively. We found a median overall survival time of 12.7 and 8.2 months for RCC and melanoma, respectively. Our study determined that a higher number of brain metastases (>5) and lower KPS were statistically significant predictors of a lower OS prognosis.

[232] Breast cancer subtype as a predictor for outcomes and control in the setting of brain metastases treated with stereotactic radiosurgery.

Journal of neuro-oncology. 2016;127(1):103-10

Grubb CS, Jani A, Wu CC, Saad S, Qureshi YH, Nanda T, Yaeh A, Rozenblat T, Sisti MB, Bruce JN, McKhann GM 2nd, Sheth SA, Lesser J, Cheng SK, Isaacson SR, Lassman AB, Connolly EP, Wang TJ

PMID: 26615564 DOI: 10.1007/s11060-015-2014-8

We investigated effects of breast cancer subtype on overall survival (OS), local and distant control, and time from initial diagnosis to brain metastases (BM). We also investigated advances in graded prognostic assessment (GPA) scores. A cohort of 72 patients treated for BM from breast cancer with Gamma Knife stereotactic radiosurgery at our institution from 2000 to 2014 had subtyping available and were used for this study. Median follow up for OS was 12 months and for control was 6 months. OS for luminal, HER2, and triple negative subtypes were 26, 20, and 22 months. OS when stratified by Sperduto et al. (*J Clin Oncol* 30(4):419-425, 2012) and Subbiah et al. (*J Clin Oncol* 33(20):2239-2245, 2015) GPAs were similar ($p = 0.087$ and $p = 0.063$). KPS and treatment modality were significant for OS ($p = 0.002$; $p = 0.034$). On univariate analysis, triple negative subtype and >3 BM were trending and significant for decreased OS ($p = 0.084$; $p = 0.047$). On multivariable analysis HER2, triple negative, and >3 BM were significant for OS ($p = 0.022$; $p = 0.040$; $p = 0.009$). Subtype was significant for response on a per lesion basis ($p = 0.007$). Subtype was trending towards significance when analyzing time from initial diagnosis to BM treatment ($p = 0.064$). Breast cancer subtype is an important prognostic factor when stratifying breast cancer patients with BM. The addition of number of BM to the GPA is a useful addition and should be further investigated. Subtype has an effect on lesion response, and also on rate of development BM after initial diagnosis.

[233] Treatment of Large Brain Metastases With Stereotactic Radiosurgery.

Technology in cancer research & treatment. 2016;15(1):186-95

Zimmerman AL, Murphy ES, Suh JH, Vogelbaum MA, Barnett GH, Angelov L, Ahluwalia M, Reddy CA, Chao ST

PMID: 25633136 DOI: 10.1177/1533034614568097

INTRODUCTION: We report our series of patients with large brain metastases, >3 cm in diameter, who received stereotactic radiosurgery (SRS) as a component of their treatment, focusing on survival and intracranial recurrence rates. **MATERIALS AND METHODS:** The brain tumor database was queried for patients treated with SRS for large brain metastases. Local recurrence (LR) and distant brain recurrence (DBR) rates were calculated using cumulative incidence analysis, and overall survival (OS) was calculated using Kaplan-Meier analysis. Patients were classified into 1 of the 4 groups

based on treatment strategy: SRS alone, surgery plus SRS, SRS plus whole-brain radiation therapy (WBRT), and salvage SRS from more remote WBRT and/or surgery. **RESULTS:** A total of 153 patients with 164 lesions were evaluated. The SRS alone was the treatment approach in 62 lesions, surgery followed by SRS to the resection bed (S + SRS) in 33, SRS + WBRT in 19, and salvage SRS in 50. There was no statistically significant difference in OS between the 4 treatment groups ($P = .06$). Median survival was highest in patients receiving surgery + SRS (12.2 months) followed by SRS + WBRT (6.9 months), SRS alone (6.6 months), and salvage SRS (6.1 months). There was also no significant difference for LR rates between the groups at 12 months. No significant variables on univariate analysis were noted for LR. The 12-month DBR rates were highest in the S + SRS group (52%), followed by salvage SRS (31%), SRS alone (28%), and SRS + WBRT (13%; $P = .03$). **CONCLUSION:** There were no significant predictors for local control. Keeping in mind that patient numbers in the SRS + WBRT group are small, the addition of WBRT to SRS did not appear to significantly improve survival or local control, supporting the delayed use of WBRT for some patients to prevent potential side effects provided regular imaging surveillance and salvage therapy are utilized. Prospective studies are needed to optimize SRS treatment regimens for patients with large brain metastases.

[234] Gamma Knife Radiosurgery in the management of single and multiple brain metastases.

Clinical neurology and neurosurgery. 2016;141:43-7

Greto D, Scoccianni S, Compagnucci A, Arilli C, Casati M, Francolini G, Cecchini S, Loi M, Desideri I, Bordi L, Bono P, Bonomo P, Meattini I, Detti B, Livi L

PMID: 26731463 DOI: 10.1016/j.clineuro.2015.12.009

OBJECTIVES: To evaluate the efficacy and safety of Gamma Knife Radiosurgery (GKRS) in the treatment of single and multiple brain metastases. **PATIENTS AND METHODS:** From October 2012 to June 2014 106 patients were treated with Radiosurgery (RS) for brain metastases at University of Florence. 77 out of 106 patients had a radiological follow up and their data were analyzed. The target was defined as the enhancing lesion. The prescription dose was defined depending on tumor volume and tumor location. Each patient performed an MRI one month after GKRS for the first three months and every 3 months thereafter. Overall survival was calculated from the day of RS until death. Local recurrence (LR) was defined as radiologic growth of the irradiated lesion, while distant brain recurrence (DBR) was the evidence of brain lesion outside the previous irradiated field. Both the LR and DBR were calculated from the RS till the day of radiological evidence of relapse. The correlations within patient and disease characteristics and the outcomes of survival and disease control were analyzed. **RESULTS:** Mean follow up was 7.2 +/- 4.8 months (range: 2.4-22.8 months). At the time of analysis 21 patients (27.3%) were dead. The overall survival (OS) at 1 year was 74%. On univariate Cox Regression analysis female gender ($p=0.043$, HR: 0.391, 95% CI: 0.157-0.972) and age >65 years ($p=0.003$ HR: 4.623, 95% CI: 1.687-12.663) were predictive for survival. On multivariate analysis, age older than 65 years ($p=0.005$ HR: 4.254, 95% CI: 1.544-11.721) was confirmed as associated with worsened overall survival. 19 patients (24.7%) had recurrence in the radiosurgery field. The median time to local failure was 4.8 +/- 2.0 months (range: 1.8-9.4 months) from GKRS. On Cox Regression univariate analysis, the only factor associated with higher risk of local failure was a number of treated lesions more than 4 ($p=0.015$, HR: 3.813, 95% CI: 1.298-11.202), no significant parameters were found at the multivariate analysis. The median time to develop distant brain failure was 6 +/- 4.32 months (range: 1.08-21.6 months). Median distant brain control was 74% at 1 year. None of the factors analyzed was statistically significant for the distant brain relapse. The radiosurgery treatment was well tolerated. One patient treated for seven metastases developed seizures 8h after GKRS, he was treated with steroids and anticonvulsants. One patient had radiologic evidence of radionecrosis without any neurological symptoms. **CONCLUSIONS:** In well-performing patients with stable systemic disease radiosurgery can be performed as an exclusive treatment for brain metastases. Younger patients could have a greater benefit from the RS, on the other hand our finding confirm no correlation between the survival outcome and the number of lesions treated.

[235] Survival but not brain metastasis response relates to lung cancer mutation status after radiosurgery.

Journal of neuro-oncology. 2016;126(3):483-91

Shin SM, Cooper BT, Chachoua A, Butler J, Donahue B, Silverman JS, Kondziolka D

PMID: 26520640 DOI: 10.1007/s11060-015-1986-8

We prospectively addressed whether EGFR and KRAS mutations, EML4-ALK, ROS1 and RET rearrangements, or wild-type (WT), affects radiosurgery outcomes and overall survival (OS) in non-small cell lung cancer (NSCLC) patients with brain metastases (BM). Of 326 patients with BM treated in 2012-2014 with Gamma Knife radiosurgery (GKRS), 112 NSCLC patients received GKRS as their initial intracranial treatment. OS, intracranial progression-free survival, and time to intracranial failure were determined. Univariate and multivariate analysis were performed to determine factors affecting OS. Toxicity of treatment was evaluated. Median follow-up was 9 months. Patients with EGFR mutant BM had improved survival compared to WT. Median time to development of BM was higher in EGFR mutant patients, but this difference was not significant (2.2 vs 0.9 months; $p = 0.2$). Median time to distant brain failure was independent of EGFR mutation status. Karnofsky performance status (KPS), non-squamous histopathology, targeted therapy, systemic disease control, EGFR mutation, and low tumor volume were predictive of increased OS on univariate analysis. KPS ($p = 0.001$) and non-squamous histopathology ($p = 0.03$) continued to be significant on multivariate analysis. Patients with EGFR mutant BM underwent salvage treatment more often than those without ($p = 0.04$). Treatment-related toxicity was no different in patients treated with GKRS combined with targeted therapies versus GKRS alone (5 vs 7%, $p = 0.7$). Patients with EGFR mutant BM had improved survival compared to a WT cohort. Intracranial disease control following radiosurgery was similar for all tumor subtypes. Radiosurgery is effective for BM and concurrent treatment with targeted therapy appears to be safe.

[236] Extended Survival and Prognostic Factors for Patients With ALK-Rearranged Non-Small-Cell Lung Cancer and Brain Metastasis.

Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2016;34(2):123-9

Johung KL, Yeh N, Desai NB, Williams TM, Lautenschlaeger T, Arvold ND, Ning MS, Attia A, Lovly CM, Goldberg S, Beal K, Yu JB, Kavanagh BD, Chiang VL, Camidge DR, Contessa JN

PMID: 26438117 DOI: 10.1200/JCO.2015.62.0138

PURPOSE: We performed a multi-institutional study to identify prognostic factors and determine outcomes for patients with ALK-rearranged non-small-cell lung cancer (NSCLC) and brain metastasis. **PATIENTS AND METHODS:** A total of 90 patients with brain metastases from ALK-rearranged NSCLC were identified from six institutions; 84 of 90 patients received radiotherapy to the brain (stereotactic radiosurgery [SRS] or whole-brain radiotherapy [WBRT]), and 86 of 90 received tyrosine kinase inhibitor (TKI) therapy. Estimates for overall (OS) and intracranial progression-free survival were determined and clinical prognostic factors were identified by Cox proportional hazards modeling. **RESULTS:** Median OS after development of brain metastases was 49.5 months (95% CI, 29.0 months to not reached), and median intracranial progression-free survival was 11.9 months (95% CI, 10.1 to 18.2 months). Forty-five percent of patients with follow-up had progressive brain metastases at death, and repeated interventions for brain metastases were common. Absence of extracranial metastases, Karnofsky performance score ≥ 90 , and no history of TKIs before development of brain metastases were associated with improved survival ($P = .003$, $< .001$, and $< .001$, respectively), whereas a single brain metastasis or initial treatment with SRS versus WBRT were not ($P = .633$ and $.666$, respectively). Prognostic factors significant by multivariable analysis were used to describe four patient groups with 2-year OS estimates of 33%, 59%, 76%, and 100%, respectively ($P < .001$). **CONCLUSION:** Patients with brain metastases from ALK-rearranged NSCLC treated with radiotherapy (SRS and/or WBRT) and TKIs have prolonged survival, suggesting that interventions to control intracranial disease are critical. The refinement of

prognosis for this molecular subtype of NSCLC identifies a population of patients likely to benefit from first-line SRS, close CNS observation, and treatment of emergent CNS disease.

[237] Leukoencephalopathy in long term brain metastases survivors treated with radiosurgery.

Journal of neuro-oncology. 2016;126(2):289-98

Cohen-Inbar O, Melmer P, Lee CC, Xu Z, Schlesinger D, Sheehan JP

PMID: 26468138 DOI: 10.1007/s11060-015-1962-3

Brain metastases (BM) develop in 10-30 % of patients. Stereotactic radiosurgery (SRS) was shown to improve local control, and performance status, in certain cohorts of brain metastasis patients. The cumulative neurocognitive effect of numerous SRS sessions remains unknown. Leukoencephalopathy is significant diffuse white matter changes and it usually implies a neurocognitive decline. We report patients with BM who survived >2 years after SRS. Clinical and treatment parameters were analyzed for development of leukoencephalopathy. Multiple parameters as well as leukoencephalopathy grade changes were recorded. The median clinical and radiological follow-up was 42 and 41 months (range 24-115 and 24-115) respectively. The cohort included 92 patients and 704 lesions. The most common malignancies were non-small cell lung carcinoma (44.5 % $n = 41$), breast adenocarcinoma (23.9 % $n = 22$) and melanoma (16.3 % $n = 15$). 27.6 % ($n = 26$) of patients underwent adjuvant WBRT. At last follow up, local tumor control was achieved in 76.3 % ($n = 61$) of patients and 71.8 % ($n = 461$) of lesions. Overall prevalence of leukoencephalopathy was 42, 60, 73 and 84 % at 1, 2, 3, and 4 years after SRS. Moderate-severe leukoencephalopathy development was related to an integral dose to skull >3 Joules ($p = 0.012$) at any radiosurgical treatment and prior WBRT ($p < 0.042$). Leukoencephalopathy incidence was consistently higher in the WBRT + SRS group at each following year of survival from initial SRS. Long-term BM survivors treated with SRS are at progressive risk for developing leukoencephalopathy. Those with a higher BM burden, higher integral SRS dose to the skull, and treatment with WBRT are at increased risk of leukoencephalopathy.

2015

[238] Use of artificial neural networks to predict the probability of developing new cerebral metastases after radiosurgery alone.

Journal of neurosurgical sciences. 2015;64(1):52-57

Azimi P, Shahzadi S, Sadeghi S

PMID: 26657134 DOI: 10.23736/S0390-5616.16.03479-2

BACKGROUND: The present study aimed to predict the probability of developing new cerebral metastases after Gamma Knife radiosurgery (GKR) alone in patients with 1-3 brain metastases by artificial neural network (ANN) model. **METHODS:** AAN and other methods were used. The AAN has been investigated in comparison of other models of analysis, including the logistic regression (LR) and the recently introduced Huttenlocher method. Patients were divided into a distant brain failure (DBF) or a distant brain control (DBC) within 6 months of follow-up. Eleven factors were determined as the input parameters for the established ANN and were trained to predict of DBF. Sensitivity analysis was performed. The ROC curve, accuracy rate, and Hosmer-Lemeshow (H-L) tests were used to assess the three different prediction methods. **RESULTS:** A total of 192 patients were categorized into the training ($N = 96$), testing ($N = 48$), and validation ($N = 48$) data sets in ANN. DBC rate was 60.4; based on the Huttenlocher classification method, it was 40.7% in Group I, 49.2% in Group II, and 88.1% in Group III. The number of cerebral metastases, primary tumor type, extra-cerebral metastases and recursive partitioning analysis (RPA) were the most important variables indicated by the ANN analysis. Compared to the other two methods, ANN model was associated to superior results: accuracy rate, 95.3%; H-L statistic, 40.9%; and AUC, 0.88%. **CONCLUSIONS:** The ANNs can be used

to effectively help for predicting DBF in patients with 1-3 brain metastasis treated with GKR alone.

[239] Leukoencephalopathy After Stereotactic Radiosurgery for Brain Metastases.

International journal of radiation oncology, biology, physics. 2015;93(4):870-8
Trifiletti DM, Lee CC, Schlesinger D, Larner JM, Xu Z, Sheehan JP
PMID: 26530756 DOI: 10.1016/j.ijrobp.2015.07.2280

PURPOSE: Although the use of stereotactic radiosurgery (SRS) in the treatment of multiple brain metastases has increased dramatically during the past decade to avoid the neurocognitive dysfunction induced by whole brain radiation therapy (WBRT), the cumulative neurocognitive effect of numerous SRS sessions remains unknown. Because leukoencephalopathy is a sensitive marker for radiation-induced central nervous system damage, we studied the clinical and dosimetric predictors of SRS-induced leukoencephalopathy. **METHODS AND MATERIALS:** Patients treated at our institution with at least 2 sessions of SRS for brain metastases from 2007 to 2013 were reviewed. The pre- and post-SRS magnetic resonance imaging sequences were reviewed and graded for white matter changes associated with radiation leukoencephalopathy using a previously validated scale. Patient characteristics and SRS dosimetric parameters were reviewed for factors that contributed to leukoencephalopathy using Cox proportional hazards modeling. **RESULTS:** A total of 103 patients meeting the inclusion criteria were identified. The overall incidence of leukoencephalopathy was 29% at year 1, 38% at year 2, and 53% at year 3. Three factors were associated with radiation-induced leukoencephalopathy: (1) the use of WBRT ($P=.019$); (2) a higher SRS integral dose to the cranium ($P=.036$); and (3) the total number of intracranial metastases ($P=.003$). **CONCLUSIONS:** Our results have established that WBRT plus SRS produces leukoencephalopathy at a much higher rate than SRS alone. In addition, for patients who did not undergo WBRT before SRS, the integral dose was associated with the development of leukoencephalopathy. As the survival of patients with central nervous system metastases increases and as the neurotoxicity of chemotherapeutic and targeted agents becomes established, these 3 potential risk factors will be important to consider.

[240] Outcome of gamma knife radiosurgery for metastatic brain tumors derived from non-small cell lung cancer.

Journal of neuro-oncology. 2015;125(2):331-8
Cho KR, Lee MH, Kong DS, Seol HJ, Nam DH, Sun JM, Ahn JS, Ahn MJ, Park K, Kim ST, Lim DH, Lee JI
PMID: 26373297 DOI: 10.1007/s11060-015-1915-x

The purpose of this study was to analyze outcomes in patients treated with gamma knife radiosurgery (GKS) for brain metastases from non-small cell lung cancer (NSCLC). We retrospectively reviewed the medical records of 817 patients who underwent GKS for brain metastases from NSCLC between January 2002 and December 2012. A total of 1363 GKS procedures were performed for 2970 lesions. The median overall survival time from the initial GKS was 13 months and the salvage treatment-free survival from the first GKS was 6.5 months. Younger age (≤ 65 years), female sex, better RPA class, higher DS-GPA score, adenocarcinoma, synchronous onset, and lower integrated value of the "numbers and cumulative volume of tumors" were associated with better outcomes. Among the 601 patients with an available follow up image, the pattern of the first progression after initial GKS was the development of new lesions in 356 patients (59.2%), regrowth of treated lesions in 106 patients (17.6%), and leptomeningeal seeding (LMS) in 51 patients (8.5%). Among the deceased, the last MRI performed prior to death was evaluated in 409 patients and showed progression in 263 patients (64.3%), despite multiple salvage treatments. LMS was identified in 63 patients (15.4%); a rate much higher than the incidence at first progression. Intracranial tumor burden, defined as the integrated value of the "number of the lesions and cumulative tumor volume", is a new prognostic factor of greater significance than tumor volume or number alone when analyzed as separate factors. Although the cause of death was not progression of brain

lesions in the majority of patients, the brain lesions tended to have been persistently progressive in most patients, despite repeated salvage treatment. LMS is an important pattern of treatment failure, in addition to local progression or development of new lesions, particularly in the terminal phase of the disease.

[241] Brainstem metastases treated with stereotactic radiosurgery: safety, efficacy, and dose response.

Journal of neuro-oncology. 2015;125(2):385-92
Trifiletti DM, Lee CC, Winardi W, Patel NV, Yen CP, Larner JM, Sheehan JP
PMID: 26341374 DOI: 10.1007/s11060-015-1927-6

The safety and efficacy of stereotactic radiosurgery (SRS) in the brainstem is questioned by some over concern of violating historical brainstem SRS dose tolerance. Our purpose was to report on the clinical outcomes of patients treated at our institution with radiosurgery for brainstem metastases. Patients with metastatic tumors within or directly abutting the brainstem from 1992 to 2014 were analyzed. Patient and tumor characteristics, SRS parameters, and toxicity were recorded and analyzed for associations with local control and survival. Multivariate statistical analysis was performed using Cox proportional hazards modeling. One-hundred and eighty-nine (189) brainstem metastases from 161 patients were included in our analysis. Whole brain irradiation was administered prior to SRS in 52% of patients. The median margin dose was 18 Gy prescribed to the 50% isodose line. Median imaging follow up was 5.4 months and median survival was 5.5 months after SRS. At last follow up, local control was achieved in 87.3% of brainstem lesions treated. There were 3 recorded events of grade 3-5 toxicity (1.8%). On multivariate analysis, a margin dose ≥ 16 Gy was associated with improved local control ($p = 0.049$) and greater KPS score was associated with improved overall survival following SRS ($p = 0.024$). Patients with brainstem metastases who have limited intracranial disease and/or who have received whole brain irradiation should be considered for SRS. Margin doses of at least 16 Gy are associated with superior local control, and serious radiation toxicity in SRS for brainstem metastasis appears rare.

[242] Stereotactic radiosurgery in the treatment of brain metastases from gastrointestinal primaries.

Journal of neuro-oncology. 2015;124(3):439-46
Trifiletti DM, Patel N, Lee CC, Romano AM, Sheehan JP
PMID: 26186901 DOI: 10.1007/s11060-015-1857-3

Brain metastases from gastrointestinal (GI) primary malignancies are generally less common than those arising from other primary locations. Our purpose was to analyze the efficacy of stereotactic radiosurgery (SRS) in the treatment of patients with brain metastases from GI malignancies in the modern radiosurgical and systemic therapy era. A review of patients treated with SRS to brain metastases from GI primaries treated from 1996 to 2015 at our institution was conducted. Clinical, therapeutic, dosimetric and radiographic characteristics were collected and analyzed for an association with brain tumor local control (LC) and overall survival (OS) following SRS using univariate and multivariate (MVA) analyses. 261 brain metastases were identified from 86 patients meeting inclusion criteria. The most common primary location was rectum ($n = 36$). LC was 94.1% at last follow up and margin dose ≥ 20 Gy was associated with improved LC on MVA ($p = 0.038$). Median OS was 6.2 months and was improved with higher performance score and luminal primary location on MVA ($p = 0.002$ and 0.015 , respectively). Tumor histology, whole brain irradiation, targeted therapies, and antineoplastic therapies were not associated with improved LC or OS on MVA. SRS provides favorable LC of brain metastases of GI origin, and margin doses of at least 20 Gy should be considered when clinically appropriate. Compared to non-luminal primaries, patients with brain metastases from a luminal primary demonstrate improved OS.

[243] Effects of an Epithelial Growth Factor Receptor-Tyrosine Kinase Inhibitor Add-on in Stereotactic Radiosurgery for Brain Metastases Originating from Non-Small-Cell Lung Cancer.

Journal of Korean Neurosurgical Society. 2015;58(3):205-10
Kim HJ, Kim WS, Kwon DH, Cho YH, Choi CM
PMID: 26539262 DOI: 10.3340/jkns.2015.58.3.205

OBJECTIVE: This study was aimed at optimizing the treatment of non-small-cell lung cancer (NSCLC) patients who are candidates for stereotactic radiosurgery (SRS) for brain metastases and harbor activating epithelial growth factor receptor (EGFR) mutations. **METHODS:** We retrospectively reviewed the medical records from 2005 to 2010 of NSCLC patients with brain metastases harboring an activating EGFR mutation. Patients who received a combination therapy of SRS and EGFR-tyrosine kinase inhibitor (TKI) for brain metastases and those who received SRS without EGFR-TKI were compared. The primary endpoint was progression-free survival (PFS) of the brain metastases. **RESULTS:** Thirty-one patients were eligible for enrolment in this study (SRS with TKI, 18; SRS without TKI, 13). Twenty-two patients (71.0%) were women and the median overall age was 56.0 years. PFS of brain lesions was not significantly prolonged in SRS with TKI treatment group than in SRS without TKI group (17.0 months vs. 9.0 months, $p=0.45$). Local tumor control rate was 83.3% in the combination therapy group, and 61.5% in the SRS monotherapy group ($p=0.23$). There were no severe adverse events related with treatment in both groups. **CONCLUSIONS:** Therapeutic outcome of concurrent SRS and TKI treatment was not superior to SRS monotherapy, however, there was no additive adverse events related with combined treatment.

[244] Control of brain metastases from radioresistant tumors treated by stereotactic radiosurgery.

Journal of neuro-oncology. 2015;124(3):507-14
Yaeh A, Nanda T, Jani A, Rozenblat T, Qureshi Y, Saad S, Lesser J, Lassman AB, Isaacson SR, Sisti MB, Bruce JN, McKhann GM 2nd, Wang TJ
PMID: 26233247 DOI: 10.1007/s11060-015-1871-5

Renal cell carcinoma, sarcoma, and melanoma are considered to be "radioresistant" tumor histologies. Brain metastases (BM) from these tumors are considered unlikely to be controlled using the relatively low doses used in whole brain radiotherapy (WBRT). Our objective was to analyze the efficacy of stereotactic radiosurgery (SRS) on local control and overall survival of BM from radioresistant primary tumors. We reviewed all patients who received Gamma Knife Radiosurgery (GKRS) for BM at Columbia University Medical Center between January 2009 and April 2014. All patients were treated using the Gamma Knife Perfexion System. Dosimetric data was collected from treatment plans and metastases were categorized as radioresistant or not. Response was assessed by reviewing follow-up brain imaging studies and classified according to RECIST. Local control and median overall survival were calculated using the Kaplan-Meier method. In total, 373 tumors were analyzed from 126 patients. Of these tumors, 49 (13.1 %) originated from radioresistant cancers. The overall local control rate in the radioresistant cohort was 89.8 and 90.1 % in the non-radioresistant cohort. Univariate and multivariate analyses demonstrated that radioresistance status of the primary tumor had no statistically significant effect on local control with hazard ratios of 1.0 ($p = 1.0$, 95 % CI 0.388-2.576) and 0.954 ($p = 0.926$, 95 % CI 0.349-2.603) respectively. Median overall survival for both radioresistant and non-radioresistant cohorts was 20.0 months, with a p value of 0.926. There was no significant difference in local control of BM from radioresistant and non-radioresistant primary tumors treated with GKRS. Both cohorts showed excellent response and local control, suggesting that SRS upfront or in addition to WBRT may be an appropriate strategy in the treatment of BM from radioresistant cancers. Median overall survival for both cohorts was equal, suggesting that improved local control may be associated with an improvement in long-term survival.

[245] Impact of systemic targeted agents on the clinical outcomes of patients with brain metastases.

Oncotarget. 2015;6(22):18945-55
Johnson AG, Ruiz J, Hughes R, Page BR, Isom S, Lucas JT, McTyre ER, Houseknecht KW, Ayala-Peacock DN, Bourland DJ, Hinson WH, Laxton AW, Tatter SB, Debinski W, Watabe K, Chan MD
PMID: 26087184 DOI: 10.18632/oncotarget.4153

BACKGROUND: To determine the clinical benefits of systemic targeted agents across multiple histologies after stereotactic radiosurgery (SRS) for brain metastases. **METHODS:** Between 2000 and 2013, 737 patients underwent upfront SRS for brain metastases. Patients were stratified by whether or not they received targeted agents with SRS. 167 (23%) received targeted agents compared to 570 (77%) that received other available treatment options. Time to event data were summarized using Kaplan-Meier plots, and the log rank test was used to determine statistical differences between groups. **RESULTS:** Patients who received SRS with targeted agents vs those that did not had improved overall survival (65% vs. 30% at 12 months, $p < 0.0001$), improved freedom from local failure (94% vs 90% at 12 months, $p = 0.06$), improved distant failure-free survival (32% vs. 18% at 12 months, $p = 0.0001$) and improved freedom from whole brain radiation (88% vs. 77% at 12 months, $p = 0.03$). Improvement in freedom from local failure was driven by improvements seen in breast cancer (100% vs 92% at 12 months, $p < 0.01$), and renal cell cancer (100% vs 88%, $p = 0.04$). Multivariate analysis revealed that use of targeted agents improved all cause mortality (HR = 0.6, $p < 0.0001$). **CONCLUSIONS:** Targeted agent use with SRS appears to improve survival and intracranial outcomes.

[246] Adverse radiation effect after stereotactic radiosurgery for brain metastases: incidence, time course, and risk factors.

Journal of neurosurgery. 2015;123(2):373-86
Sneed PK, Mendez J, Vemer-van den Hoek JG, Seymour ZA, Ma L, Molinaro AM, Fogh SE, Nakamura JL, McDermott MW
PMID: 25978710 DOI: 10.3171/2014.10.JNS141610

OBJECT: The authors sought to determine the incidence, time course, and risk factors for overall adverse radiation effect (ARE) and symptomatic ARE after stereotactic radiosurgery (SRS) for brain metastases. **METHODS:** All cases of brain metastases treated from 1998 through 2009 with Gamma Knife SRS at UCSF were considered. Cases with less than 3 months of follow-up imaging, a gap of more than 8 months in imaging during the 1st year, or inadequate imaging availability were excluded. Brain scans and pathology reports were reviewed to ensure consistent scoring of dates of ARE, treatment failure, or both; in case of uncertainty, the cause of lesion worsening was scored as indeterminate. Cumulative incidence of ARE and failure were estimated with the Kaplan-Meier method with censoring at last imaging. Univariate and multivariate Cox proportional hazards analyses were performed. **RESULTS:** Among 435 patients and 2200 brain metastases evaluable, the median patient survival time was 17.4 months and the median lesion imaging follow-up was 9.9 months. Calculated on the basis of 2200 evaluable lesions, the rates of treatment failure, ARE, concurrent failure and ARE, and lesion worsening with indeterminate cause were 9.2%, 5.4%, 1.4%, and 4.1%, respectively. Among 118 cases of ARE, approximately 60% were symptomatic and 85% occurred 3-18 months after SRS (median 7.2 months). For 99 ARE cases managed without surgery or bevacizumab, the probabilities of improvement observed on imaging were 40%, 57%, and 76% at 6, 12, and 18 months after onset of ARE. The most important risk factors for ARE included prior SRS to the same lesion (with 20% 1-year risk of symptomatic ARE vs 3%, 4%, and 8% for no prior treatment, prior whole brain radiotherapy [WBRT], or concurrent WBRT) and any of these volume parameters: target, prescription isodose, 12-Gy, or 10-Gy volume. Excluding lesions treated with repeat SRS, the 1-year probabilities of ARE were < 1%, 1%, 3%, 10%, and 14% for maximum diameter 0.3-0.6 cm, 0.7-1.0 cm, 1.1-1.5 cm, 1.6-2.0 cm, and 2.1-5.1 cm, respectively. The 1-year probabilities of symptomatic ARE leveled off at 13%-14% for brain metastases maximum diameter > 2.1 cm, target volume > 1.2 cm³, prescription

isodose volume > 1.8 cm(3), 12-Gy volume > 3.3 cm(3), and 10-Gy volume > 4.3 cm(3), excluding lesions treated with repeat SRS. On both univariate and multivariate analysis, capecitabine, but not other systemic therapy within 1 month of SRS, appeared to increase ARE risk. For the multivariate analysis considering only metastases with target volume > 1.0 cm(3), risk factors for ARE included prior SRS, kidney primary tumor, connective tissue disorder, and capecitabine. **CONCLUSIONS:** Although incidence of ARE after SRS was low overall, risk increased rapidly with size and volume, leveling off at a 1-year cumulative incidence of 13%-14%. This study describes the time course of ARE and provides risk estimates by various lesion characteristics and treatment parameters to aid in decision-making and patient counseling.

[247] Competing Risk Analysis of Neurologic versus Nonneurologic Death in Patients Undergoing Radiosurgical Salvage After Whole-Brain Radiation Therapy Failure: Who Actually Dies of Their Brain Metastases?

International journal of radiation oncology, biology, physics. 2015;92(5):1008-1015
Lucas JT Jr, Colmer HG 4th, White L, Fitzgerald N, Isom S, Bourland JD, Laxton AW, Tatter SB, Chan MD

PMID: 26050609 DOI: 10.1016/j.ijrobp.2015.04.032

PURPOSE: To estimate the hazard for neurologic (central nervous system, CNS) and nonneurologic (non-CNS) death associated with patient, treatment, and systemic disease status in patients receiving stereotactic radiosurgery after whole-brain radiation therapy (WBRT) failure, using a competing risk model. **PATIENTS AND METHODS:** Of 757 patients, 293 experienced recurrence or new metastasis following WBRT. Univariate Cox proportional hazards regression identified covariates for consideration in the multivariate model. Competing risks multivariable regression was performed to estimate the adjusted hazard ratio (aHR) and 95% confidence interval (CI) for both CNS and non-CNS death after adjusting for patient, disease, and treatment factors. The resultant model was converted into an online calculator for ease of clinical use. **RESULTS:** The cumulative incidence of CNS and non-CNS death at 6 and 12 months was 20.6% and 21.6%, and 34.4% and 35%, respectively. Patients with melanoma histology (relative to breast) (aHR 2.7, 95% CI 1.5-5.0), brainstem location (aHR 2.1, 95% CI 1.3-3.5), and number of metastases (aHR 1.09, 95% CI 1.04-1.2) had increased aHR for CNS death. Progressive systemic disease (aHR 0.55, 95% CI 0.4-0.8) and increasing lowest margin dose (aHR 0.97, 95% CI 0.9-0.99) were protective against CNS death. Patients with lung histology (aHR 1.3, 95% CI 1.1-1.9) and progressive systemic disease (aHR 2.14, 95% CI 1.5-3.0) had increased aHR for non-CNS death. **CONCLUSION:** Our nomogram provides individual estimates of neurologic death after salvage stereotactic radiosurgery for patients who have failed prior WBRT, based on histology, neuroanatomical location, age, lowest margin dose, and number of metastases after adjusting for their competing risk of death from other causes.

[248] The Energy Index Does Not Affect Local Control of Brain Metastases Treated by Gamma Knife Stereotactic Radiosurgery.

Neurosurgery. 2015;77(1):119-25; discussion 125
Jani A, Rozenblat T, Yaeh AM, Nanda T, Saad S, Qureshi YH, Feng W, Sisti MB, Bruce JN, McKhann GM 2nd, Lesser J, Lassman AB, Isaacson SR, Wang TJ
PMID: 25830600 DOI: 10.1227/NEU.0000000000000750

BACKGROUND: The energy index (EI) is a measure of dose homogeneity within a target volume calculated by the integral dose divided by the product of prescription dose and tumor volume. **OBJECTIVE:** To assess whether a higher EI is associated with greater local control for brain metastases (BMs) treated by Gamma Knife radiosurgery (GKRS). **METHODS:** We reviewed all patients treated with GKRS for BM at our institution between January 2009 and February 2014. Data on the prescription dose, prescription isodose line, minimum dose, mean dose, integral dose, tumor volume, and EI were collected. Tumor response was assessed by reviewing follow-up brain imaging studies and classified according to the Response Evaluation Criteria in Solid Tumors. Local control per lesion and dosimetric prognostic factors for local control were assessed by univariate and

multivariate Cox proportional hazards regression analyses. **RESULTS:** Of 213 patients treated, 126 had follow-up imaging available with a median follow-up of 6 months. Three hundred seventy-three individual tumors were analyzed. Of these, 133 showed a complete response, 157 showed a partial response, 46 remained stable, and 37 developed local failure. Tumors with EI ≥ 1.6 mJ.mL(-1).Gy(-1) showed a higher rate of complete response. Local control rates at 6, 11, and 17 months were 95.4%, 86.5%, and 81.5%, respectively. On univariate analysis, the following factors were associated with higher rates of local failure: prescription doses of 16 and 18 Gy compared with a prescription dose of 20 Gy. The following factors were associated with a greater rate of local control: maximum dose and mean dose. On multivariate analysis, the only statistically significant factor associated with a greater rate of local failure was prescription dose of 16 Gy compared with 20 Gy. **CONCLUSION:** GKRS for BM results in a high rate of local control with an 11-month rate of 86.5%. A higher EI was not significantly associated with a higher rate of local control on multivariate analysis. Prescription dose was found to be the only significant predictor of local control on multivariate analysis.

[249] Does lung cancer mutation status and targeted therapy predict for outcomes and local control in the setting of brain metastases treated with radiation?

Neuro-oncology. 2015;17(7):1022-8
Wang TJ, Saad S, Qureshi YH, Jani A, Nanda T, Yaeh AM, Rozenblat T, Sisti MB, Bruce JN, McKhann GM, Lesser J, Halmos B, Stoopler MB, Lassman AB, Cheng SK, Isaacson SR
PMID: 25910841 DOI: 10.1093/neuonc/nov043

BACKGROUND: We investigated effects of genetic alterations in epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and Kirsten rat sarcoma viral oncogene homolog (KRAS) on overall survival (OS) and local control after stereotactic radiosurgery for brain metastases in non-small cell lung cancer (NSCLC). **METHODS:** A cohort of 89 out of 262 NSCLC patients (2003-2013) treated with gamma knife radiosurgery for brain metastases had genotyping available and were selected as our study population. **RESULTS:** Median follow-up was 12 months. Median OS rates for the EGFR, KRAS, echinoderm microtubule-associated protein-like 4 (EML4)-ALK mutated, and wild-type cohorts were 17, 7, 27, and 12 months, respectively (P = .019), and for targeted versus nontargeted therapy 21 and 11 months, respectively (P = .071). Targeted therapy was a strong predictor of increased OS on univariate (P = .037) and multivariate (P = .022) analysis. Gender, primary tumor controlled status, recursive partitioning analysis class, and graded prognostic assessment score were associated with OS (P < .05). On multivariate analysis, positive EGFR mutational status was a highly significant predictor for decreased survival (hazard ratio: 8.2; 95% CI: 2.0-33.7; P = .003). However, when we recategorized EGFR-mutant cases based on whether they received tyrosine kinase inhibitor, OS was no longer significantly shorter (hazard ratio: 1.5; P = .471). Median OS for patients with and without local failure was 17 and 12 months, respectively (P = .577). Local failure rates for EGFR, KRAS, EML4-ALK mutated, and wild-type cohorts by lesion were 8.7%, 5.4%, 4.3%, and 5.1%, respectively. **CONCLUSIONS:** This study suggests that EGFR tyrosine kinase mutation and ALK translocation results in improved survival to targeted therapies and that mutation status itself does not predict survival and local control in patients with brain metastases from NSCLC.

[250] Outcomes and predictors of improved survival after gamma knife radiosurgery for metastatic brain tumors originated from breast carcinoma.

Neurosurgical review. 2015;38(3):489-98; discussion 498
Bir SC, Bollam P, Nanda A
PMID: 25843300 DOI: 10.1007/s10143-015-0624-4
Gamma knife radiosurgery (GKRS) has emerged as a possible treatment option for metastasis brain tumor (MBTs) originated from breast cancer. However, the intermediate or long-term outcome of GKRS on MBTs originated from breast carcinoma is not well defined. The outcome of GKRS on MBTs derived from

breast carcinoma was reviewed in our institution's case series. We performed a retrospective review (2000-2013) of 50 patients with MBTs originated from breast cancer who received GKRS. Out of 50 patients, 11 patients had recurrent tumors after microsurgical resection and the other 39 patients received GKRS alone. The study population was followed clinically and radiographically after GKRS treatment. GKRS on MBTs metastasized from breast cancer showed significant variations in tumor growth control (decreased in 14 (31.9 %) patients, arrested growth in 17 (38.6 %) patients, and progressed tumor in 13 (29.5 %) patients). The overall median survival in this case series was 33 months. In our case series, overall survival rate after 5 years was 20 %, whereas progression-free survival rate after 5 years was 30 %. The prognostic factors for improving survival in the patients with MBTs from breast cancer were recursive partitioning analysis (RPA) class I ($p = 0.014$), age ≤ 65 years ($p = 0.025$), controlled primary tumor ($p = 0.04$), and single number of MBTs ($p = 0.022$). Recent follow-up revealed that GKRS offers good overall survival period in both new and recurrent patients with MBTs originated from breast carcinoma. Thus, GKRS is a therapeutic option for new and recurrent patients with MBTs derived from breast cancer.

[251] Stereotactic Radiosurgery With or Without Whole-Brain Radiotherapy for Brain Metastases: Secondary Analysis of the JROSG 99-1 Randomized Clinical Trial.

JAMA oncology. 2015;1(4):457-64

Aoyama H, Tago M, Shirato H

PMID: 26181254 DOI: 10.1001/jamaoncol.2015.1145

IMPORTANCE: It remains uncertain whether treatment with stereotactic radiosurgery (SRS) alone can be safely applied to all patient populations with 1 to 4 brain metastases (BMs) exhibiting heterogeneous prognoses. **OBJECTIVE:** To investigate the feasibility of SRS alone for patients with different prognoses determined by the diagnosis-specific Graded Prognostic Assessment (DS-GPA). **DESIGN, SETTING, AND PARTICIPANTS:** A secondary analysis (performed in September 2014) of the Japanese Radiation Oncology Study Group (JROSG) 99-1, a phase 3 randomized trial, comparing SRS alone and whole-brain radiotherapy (WBRT) + SRS conducted in 1999 to 2003. Among a total of 132 patients, 88 with non-small-cell lung cancer (NSCLC) and 1 to 4 BMs were included and poststratified by DS-GPA scores to avoid potential bias from BMs from different primary cancer types. The median follow-up time was 8.05 months. **INTERVENTIONS:** The WBRT schedule was 30 Gy in 10 fractions over 2 to 2.5 weeks. The mean SRS dose was 21.9 Gy in SRS alone and 16.6 Gy in WBRT + SRS. **MAIN OUTCOMES AND MEASURES:** The primary end point was overall survival (OS), and the secondary end points included brain tumor recurrence (BTR), salvage treatment, and radiation toxic effects. **RESULTS:** Forty-seven patients had a favorable prognosis, with DS-GPA scores of 2.5 to 4.0 (26 SRS-alone and 21 WBRT + SRS [DS-GPA 2.5-4.0 group]), and 41 had an unfavorable prognosis, with DS-GPA scores of 0.5 to 2.0 (19 SRS-alone and 22 WBRT + SRS [DS-GPA 0.5-2.0 group]). Significantly better OS was observed in the DS-GPA 2.5-4.0 group in WBRT + SRS vs the SRS alone, with a median survival time of 16.7 (95% CI, 7.5-72.9) months vs 10.6 (95% CI, 7.7-15.5) months ($P = .04$) (hazard ratio [HR], 1.92; 95% CI, 1.01-3.78). However, no such difference was observed in the DS-GPA 0.5-2.0 group (HR, 1.05; 95% CI, 0.55-1.99) ($P = .86$). This benefit could be explained by the differing BTR rates, in that the prevention against BTR by WBRT had a more significant impact in the DS-GPA 2.5-4.0 group (HR, 8.31; 95% CI, 3.05-29.13) ($P < .001$) vs the DS-GPA 0.5-2.0 group (HR, 3.57; 95% CI, 1.02-16.49) ($P = .04$). **CONCLUSIONS AND RELEVANCE:** Despite the current trend of using SRS alone, the important role of WBRT for patients with BMs from NSCLC with a favorable prognosis should be considered. Our findings should be validated through appropriately designed prospective studies. **TRIAL REGISTRATION:** umin.ac.jp/ctr Identifier: C000000412.

[252] Survival of patients with multiple brain metastases treated with whole-brain radiotherapy.

CNS oncology. 2015;4(4):213-24

Wong E, Tsao M, Zhang L, Danjoux C, Barnes E, Pulenzas N, Vuong S, Chow E
PMID: 26118428 DOI: 10.2217/cns.15.17

AIM: To report the survival outcomes of patients with multiple brain metastases treated with whole-brain radiotherapy. **PATIENTS & METHODS:** From 2004 to 2012, patients with brain metastases treated with whole-brain radiotherapy were included. Overall survival (OS) was calculated from the start of radiation treatment. Univariate and multivariate proportional hazard model of OS was conducted. Generalized R(2) statistic (ranged from 0 to 1) was calculated to determine the association with the outcome. **RESULTS:** Nine-hundred-ninety-one patients were included. The actuarial median OS time was 2.7 months (95% CI: 2.5-2.9). Patients of older age (>65 years), lower Karnofsky performance status, not postoperative and patients with gastrointestinal, genitourinary or lung as opposed to breast cancer were more likely to have a shorter survival. **CONCLUSION:** Short median survival of 2.7 months may reflect poorer prognosis of patients referred due to large amount of referrals for radiosurgery. Prognostic factors for survival should be considered at consultation.

[253] Stereotactic radiosurgery to the resection cavity for brain metastases: prognostic factors and outcomes.

Journal of radiosurgery and SBRT. 2015;3(3):179-186

Abel RJ, Ji L, Yu C, Lederman A, Chen T, Liu C, Zada G, Kim PE, Apuzzo M, Chang EL

PMID: 29296400 DOI:

BACKGROUND: Adjuvant stereotactic radiosurgery (SRS) alone after surgical resection is increasingly being used to provide excellent local control while avoiding the side effects of whole brain radiation therapy (WBRT). We report our ten year experience using this treatment scheme. **PURPOSE/OBJECTIVES:** To determine the rates and any correlates of local control, distant brain failure, and overall survival using SRS alone to the resection cavity. **MATERIALS/METHODS:** We performed a retrospective analysis of 509 patients with brain metastasis who underwent Gamma Knife SRS at our institution between 2003 and 2013. Of this group 85 patients were identified that had resection of the metastasis and subsequent SRS to the cavity. Mean dose to the resection cavity was 17.3 Gy (range 14-20) to an average volume of 12cc (range 0.3-83cc). Multiple patient, tumor, and treatment specific factors were collected for analysis (see Table 1). Vital statistics were provided by our institution's tumor registry. The primary endpoint of our analyses was recurrence free survival (RFS); defined as the duration in time between the date of SRS and any local or distant brain tumor recurrence. **RESULTS:** With a median follow up of 16.4 months, the overall local and distant brain failure at 12 months was 13% (95%CI 5%-21%) and 51% (95%CI 37%-64%) respectively. RPA was class 1 (5%), 2 (75%), and 3 (20%). The median overall survival (OS) was 20 months. The median RFS was 24 months with radiosensitive tumors: non small cell lung cancer ($n=12$), breast ($n=16$), gastrointestinal ($n=7$), small cell lung cancer ($n=1$), and other ($n=9$) compared to 5.6 months ($p=0.006$) in radioresistant tumors: melanoma ($n=33$), sarcoma ($n=1$), and renal cell carcinoma ($n=6$). Median OS for radioresistant and radiosensitive patients was 12 vs 25 months respectively ($p=0.11$). Additionally, there was a significant improved survival difference seen amongst those who had a gross total resection (GTR, $n=46$) compared to a sub total resection ($n=39$) with median OS of 27 vs 16 months ($p=0.020$) respectively. Radiographic changes suggestive of radiation necrosis were present in 6 patients, 2 of which were determined histopathologically after surgical intervention. Due to the limited number of local recurrence events ($n=10$), there was insufficient power to analyze prognostic factors for local recurrence. **CONCLUSIONS:** Our results compare favorably with multiple other institution experiences showing excellent local control with SRS to the resection cavity following resection. Radioresistant histologies were associated with a worse RFS. Patients undergoing GTR had a significantly longer OS than those with STR. At our institution we continue to offer patients SRS to

the resection cavity for those with good performance status and limited brain metastases.

[254] Factors that determine local control with gamma knife radiosurgery: The role of primary histology.

Journal of radiosurgery and SBRT. 2015;3(4):281-286

Black PJ, Page BR, Lucas JT Jr, Hughes RT, Laxton AW, Tatter SB, Munley MT, Chan MD

PMID: 26478823 DOI:

BACKGROUND: Stereotactic radiosurgery for the treatment of brain metastases is commonly delivered without regard to primary cancer histology. This study sought to determine if the primary site of origin for brain metastases affected the propensity for local failure. **METHODS:** A total of 83 patients with 200 brain metastases were examined retrospectively for predictors of infield failure. Tumor, patient, and treatment characteristics were analyzed including primary tumor histology, radiosurgical dose and age. Cox proportional hazards models, univariate and multivariate analyses were used to identify predictors of local failure. **RESULTS:** Freedom from local failure for the entire population was 83% and 65% at 6 and 12 months, respectively. Multivariate analysis revealed that breast cancer brain metastases have a significantly lower risk of local failure than melanoma (HR = 0.31, $p < 0.001$). Additionally, multivariate analysis revealed that increasing dose lowered risk for local failure (HR = 0.87, $p < 0.001$). **CONCLUSIONS:** Melanoma histology leads to a higher rate of local failure. Higher prescription dose results in higher incidence of local control.

[255] Prognostic significance of EGFR and KRAS mutations in NSCLC patients with brain metastases treated with radiosurgery(dagger).

Journal of radiosurgery and SBRT. 2015;3(3):171-178

Parikh NR, Likhacheva A, Pinnix C, Allen PK, Prabhu SS, Guha-Thakurta N, Welsh JW, Brown PD, Chang EL

PMID: 29296399 DOI:

PURPOSE: Determine whether EGFR and KRAS mutations carry prognostic significance in non-small cell lung cancer (NSCLC) patients with brain metastases treated with stereotactic radiosurgery. **METHODS AND MATERIALS:** Ninety-four NSCLC patients with brain metastases initially treated with stereotactic radiosurgery were retrospectively reviewed. Both EGFR and KRAS mutation status were recorded in 67 patients: EGFR+/KRAS- status in 9 patients, EGFR-/KRAS+ in 15 patients, and EGFR-/KRAS- in 43 patients. Survival was determined using the Kaplan-Meier method. Cox regression was used to assess the effects of patient factors on overall survival, local control, and distant brain control - all from time of brain metastasis diagnosis. **RESULTS:** Median overall survival from time of brain metastasis diagnosis was 30.6 months for EGFR+/KRAS- patients, 9.8 months for EGFR-/KRAS+ patients, and 19.1 months for EGFR-/KRAS- patients ($p = 0.094$). Local control at 2 years was 100% for EGFR+/KRAS- patients, 66.7% for EGFR-/KRAS+ patients, and 97.2% for EGFR-/KRAS- patients ($p = 0.399$). Distant brain control at 12 months was achieved in 66.7% of EGFR+/KRAS- patients, 30.0% of EGFR-/KRAS+ patients, and 73.7% of EGFR-/KRAS- patients ($p = 0.039$). On multivariate analysis, the most important predictors of mortality were baseline DS-GPA > 2 (HR=0.27; $p = 0.001$), EGFR mutation positivity (HR=0.30; $p = 0.054$), and KRAS mutation positivity (HR=2.12; $p = 0.056$); the most important predictors of distant brain failure were KRAS status (HR=4.44; $p = 0.004$) and extracranial disease (HR=3.28; $p = 0.058$); there was no statistically significant multivariate model identified for local control. **CONCLUSIONS:** In NSCLC patients with brain metastases, KRAS mutations portend higher rates of distant brain failure. Our data also suggests that EGFR portends better overall survival and KRAS portends worse overall survival, though this still needs to be verified by a larger study.

[256] Predictors for long-term survival free from whole brain radiation therapy in patients treated with radiosurgery for limited brain metastases.

Frontiers in oncology. 2015;5:110

Gorovets D, Rava P, Ebner DK, Tybor DJ, Cielo D, Puthawala Y, Kinsella TJ,

DiPetrillo TA, Wazer DE, Hepel JT

PMID: 26029666 DOI: 10.3389/fonc.2015.00110

PURPOSE: To identify predictors for prolonged survival free from salvage whole brain radiation therapy (WBRT) in patients with brain metastases treated with stereotactic radiosurgery (SRS) as their initial radiotherapy approach. **MATERIALS AND METHODS:** Patients with brain metastases treated with SRS from 2001 to 2013 at our institution were identified. SRS without WBRT was typically offered to patients with 1-4 brain metastases, Karnofsky performance status ≥ 70 , and life expectancy ≥ 3 months. Three hundred and eight patients met inclusion criteria for analysis. Medical records were reviewed for patient, disease, and treatment information. Two comparison groups were identified: those with ≥ 1 -year WBRT-free survival (N = 104), and those who died or required salvage WBRT within 3 months of SRS (N = 56). Differences between these groups were assessed by univariate and multivariate analyses. **RESULTS:** Median survival for all patients was 11 months. Among patients with ≥ 1 -year WBRT-free survival, median survival was 33 months (12-107 months) with only 21% requiring salvage WBRT. Factors significantly associated with prolonged WBRT-free survival on univariate analysis ($p < 0.05$) included younger age, asymptomatic presentation, RTOG RPA class I, fewer brain metastases, surgical resection, breast primary, new or controlled primary, absence of extracranial metastatic disease, and oligometastatic disease burden (≤ 5 metastatic lesions). After controlling for covariates, asymptomatic presentation, breast primary, single brain metastasis, absence of extracranial metastases, and oligometastatic disease burden remained independent predictors for favorable WBRT-free survival. **CONCLUSION:** A subset of patients with brain metastases can achieve long-term survival after upfront SRS without the need for salvage WBRT. Predictors identified in this study can help select patients that might benefit most from a treatment strategy of SRS alone.

[257] Comparison Between Surgical Resection and Stereotactic Radiosurgery in Patients with a Single Brain Metastasis from Non-Small Cell Lung Cancer.

World neurosurgery. 2015;83(6):900-6

Bougie E, Masson-Cote L, Mathieu D

PMID: 25659803 DOI: 10.1016/j.wneu.2015.01.029

BACKGROUND: The management of patients with single brain metastasis (BM) from non-small cell lung cancer (NSCLC) is controversial. Surgical resection (SR) with adjuvant irradiation and stereotactic radiosurgery (SRS) are performed in the treatment of such lesions. This study compared both modalities in terms of tumor control and survival. **METHODS:** During the period 2004-2011, 115 patients with single BM from NSCLC were treated with SR or SRS at our institution. Median patient age was 61 years. SR was performed in 43 patients, and SRS was performed in 72 patients. Most patients who underwent SR had adjuvant irradiation. Of patients, 63% in the SR group and 56% in the SRS group had synchronous presentation of BM and lung primary tumor. Thoracic disease was managed with curative intent in 60% of patients in the SR group compared with 50% of patients in the SRS group. **RESULTS:** Median follow-up was 10.2 months. Local control was 72% in patients in the SR group and 79% in patients in the SRS group ($P = 0.992$). Median survival for patients in the SR group was 13.3 months, and median survival for patients in the SRS group was 7.8 months ($P = 0.047$). Multivariate analyses revealed aggressive treatment of the primary NSCLC as an independent factor associated with prolonged survival in patients undergoing SR. In the SRS group, patients with metachronous metastasis showed a better prognosis. Metachronous presentation was associated with more aggressive management of the primary tumor. **CONCLUSIONS:** In this study, patients with single BM undergoing SR had a survival advantage. However, because SR and SRS achieved comparable local control of BM, patients receiving SRS should benefit from an equally aggressive treatment of the primary NSCLC, as thoracic management was the most important predictor of survival.

[258] Estimating the additive benefit of surgical excision to stereotactic radiosurgery in the management of metastatic brain disease.

Neurosurgery. 2015;76(6):707-12; discussion 712-3

Quigley MR, Bello N, Jho D, Fuhrer R, Karlovits S, Buchinsky FJ
PMID: 25734321 DOI: 10.1227/NEU.0000000000000707

BACKGROUND: There are limited data on the benefits of surgical tumor resection plus stereotactic radiosurgery (SRS) in comparison with SRS alone for patients with oligometastatic brain disease. **OBJECTIVE:** To determine the benefit of adding resection to SRS. **METHODS:** We reviewed 162 consecutive patients with oligometastatic brain disease, who underwent surgical tumor resection and SRS boost (n = 49) or SRS alone (n = 113). Patients receiving prior whole brain radiation therapy were excluded. Factors related to patient survival and time-to-local recurrence (TTLR) were determined by Cox regression. The effect of complete resection + SRS boost on survival was further explored by propensity score matching. **RESULTS:** The average age of the cohort was 65.3 years, it was 49.4% female, and included 260 brain tumors, of which 119 tumors were single. Seventy-three brain tumors recurred (28%). TTLR was related to radiation-sensitive pathology (hazards ratio [HR] = 0.34, P = .001), treatment volume (HR = 1.078/mL, P = .002), and complete tumor resection (HR = 0.37, P = .015). Factors related to survival were age (HR = 1.21/decade, P = .037), Eastern Cooperative Oncology Group performance score (HR = 1.9, P = .001), and complete surgical resection (HR = 0.55, P = .01). Propensity score matched analysis of complete surgical resection + SRS boost (n = 40) vs SRS alone (n = 80) yielded nearly identical survival results (HR = 0.52, P = .030) compared with the initial unmatched sample. Incomplete tumor resection had both median survival and TTLR equivalent to SRS alone. **CONCLUSION:** Complete surgical resection + SRS boost is associated with improved survival and reduced likelihood of local tumor recurrence in comparison with SRS alone. Incomplete resection did not improve survival or TTLR compared with SRS alone.

[259] A randomized phase III trial of stereotactic radiosurgery (SRS) versus observation for patients with asymptomatic cerebral oligo-metastases in non-small-cell lung cancer.

Annals of oncology : official journal of the European Society for Medical Oncology. 2015;26(4):762-768

Lim SH, Lee JY, Lee MY, Kim HS, Lee J, Sun JM, Ahn JS, Um SW, Kim H, Kim BS, Kim ST, Na DL, Sun JY, Jung SH, Park K, Kwon OJ, Lee JI, Ahn MJ
PMID: 25538174 DOI: 10.1093/annonc/mdu584

BACKGROUND: It is unclear whether treating brain metastasis before starting systemic chemotherapy can improve survival compared with upfront chemotherapy in non-small-cell lung cancer (NSCLC) with asymptomatic cerebral oligo-metastases. **PATIENTS AND METHODS:** We undertook a randomized, controlled trial of 105 patients with one to four brain metastases, admitted to Samsung Medical Center between 2008 and 2013. Patients were randomly assigned to receive stereotactic radiosurgery (SRS) (49 patients) followed by chemotherapy or upfront chemotherapy (49 patients). The primary end point was overall survival (OS) and secondary end points included central nervous system (CNS) progression-free survival, progression to symptomatic brain metastasis and brain functional outcome. **RESULTS:** The median age was 58 years (range, 29-85) with ECOG 0-1 performance status, and 40% of patients were never smokers. Most patients had adenocarcinoma, and about half of patients had only one brain metastasis, while the rest had multiple cerebral metastases. The median OS time was 14.6 months [95% confidence interval (CI), 9.2-20.0] in the SRS group and 15.3 months (95% CI, 7.2-23.4) for the upfront chemotherapy group (P = 0.418). There was no significant difference in time to CNS disease progression [median, 9.4 months (SRS) versus 6.6 months (upfront chemotherapy), P = 0.248]. Symptomatic progression of brain metastases was observed more frequently in the upfront chemotherapy group (26.5%) than the SRS group (18.4%) but without statistical significance. **CONCLUSIONS:** Although this study included smaller sample size than initially anticipated due to early termination, SRS followed by chemotherapy did not improve OS in oligo-brain metastases NSCLC patients compared with upfront chemotherapy. Further study with large number of patients should be needed to confirm the use of upfront chemotherapy alone in this subgroup of patients. CLINICAL TRIALS NUMBER: NCT01301560.

[260] Tumor progression in patients receiving adjuvant whole-brain radiotherapy vs localized radiotherapy after surgical resection of brain metastases.

Neurosurgery. 2015;76(4):411-20

Hsieh J, Elson P, Otvos B, Rose J, Loftus C, Rahmathulla G, Angelov L, Barnett GH, Weil RJ, Vogelbaum MA

PMID: 25599198 DOI: 10.1227/NEU.0000000000000626

BACKGROUND: Surgery followed by adjuvant radiotherapy is a well-established treatment paradigm for brain metastases. **OBJECTIVE:** To examine the effect of postsurgical whole-brain radiotherapy (WBRT) or localized radiotherapy (LRT), including stereotactic radiosurgery and intraoperative radiotherapy, on the rate of recurrence both local and distal to the resection site in the treatment of brain metastases. **METHODS:** We retrospectively identified patients who underwent surgery for brain metastasis at the Cleveland Clinic between 2004 and 2012. Institutional review board-approved chart review was conducted, and patients who had radiation before surgery, who had nonmetastatic lesions, or who lacked postadjuvant imaging were excluded. **RESULTS:** The final analysis included 212 patients. One hundred fifty-six patients received WBRT, 37 received stereotactic radiosurgery only, and 19 received intraoperative radiotherapy. One hundred forty-six patients were deceased, of whom 60 (41%) died with no evidence of recurrence. Competing risks methodology was used to test the association between adjuvant modality and progression. Multivariable analysis revealed no significant difference in the rate of recurrence at the resection site (hazard ratio [HR] 1.46, P = .26) or of unresected, radiotherapy-treated lesions (HR 1.70, P = .41) for LRT vs WBRT. Patients treated with LRT had an increased hazard of the development of new lesions (HR 2.41, P < .001) and leptomeningeal disease (HR 2.45, P = .04). Median survival was 16.5 months and was not significantly different between groups. **CONCLUSION:** LRT as adjuvant treatment to surgical resection of brain metastases is associated with an increased rate of development of new distant metastases and leptomeningeal disease compared with WBRT, but not with recurrence at the resection site or of unresected lesions treated with radiation.

[261] Gamma knife radiosurgery for the management of cerebral metastases from non-small cell lung cancer.

Journal of neurosurgery. 2015;122(4):766-72

Bowden G, Kano H, Caparosa E, Park SH, Niranjan A, Flickinger J, Lunsford LD
PMID: 25658792 DOI: 10.3171/2014.12.JNS141111

OBJECT: Non-small cell lung cancer (NSCLC) is the most frequent cancer that metastasizes to brain. Stereotactic radiosurgery (SRS) has become the management of choice for most patients with such metastatic tumors. Therefore, the authors endeavored to elucidate the survival and SRS outcomes for patients with NSCLC metastasis at their center. **METHODS:** In this single-institution retrospective analysis, the authors reviewed their experience with NSCLC metastasis during a 10-year period from 2001 to 2010. Seven hundred twenty patients underwent Gamma Knife radiosurgery. A total of 1004 SRS procedures were performed, and 3143 tumors were treated. The NSCLC subtype was adenocarcinoma in 386 patients, squamous cell carcinoma in 111 patients, and large cell carcinoma in 34 patients. The median aggregate tumor volume was 4.5 cm³ (range 0.1-88 cm³). **RESULTS:** The median survival time after diagnosis of brain metastasis from NSCLC was 12.6 months, and the median survival after SRS was 8.5 months. The 1-, 2-, and 5-year survival rates after SRS were 39%, 21%, and 10%, respectively. Postradiosurgery survival was decreased in patients treated with prior whole-brain radiation therapy compared with SRS alone (p = 0.003). Aggregate tumor volume was inversely related to survival after SRS (p < 0.001), and the histological subgroups demonstrated significant survival differences (p = 0.023). The overall local tumor control rate in the entire group was 92.8%. One hundred seventy-four patients (24%) underwent repeat SRS for new or resistant metastatic deposits. **CONCLUSIONS:** Stereotactic radiosurgery is an effective means of providing local control for NSCLC metastases. Neurological function and survival benefit from serial patient monitoring and repeat SRS for new tumors.

[262] Outcomes of gamma knife radiosurgery, bi-modality & tri-modality treatment regimens for patients with one or multiple brain metastases: the Columbia University Medical Center experience.

Journal of neuro-oncology. 2015;122(2):399-408

Wang TJ, Saad S, Qureshi YH, Jani A, Isaacson SR, Sisti MB, Bruce JN, McKhann GM 2nd, Lesser J, Cheng SK, Clifford Chao KS, Lassman AB
PMID: 25687652 DOI: 10.1007/s11060-015-1728-y

Optimal treatment of brain metastases (BMs) is debatable. However, surgery or gamma knife radiosurgery (GKRS) improves survival when combined with whole brain radiotherapy (WBRT) versus WBRT alone. We retrospectively reviewed an institutional database of patients treated with GKRS for BMs from 1998 to 2013 to explore effects of single or multi-modality therapies on survival. There were 528 patients with median age 62 years. Histologies included 257 lung, 102 breast, 62 melanoma, 40 renal cell, 29 gastrointestinal, and 38 other primary cancers. Treatments included: 206 GKRS alone, 111 GKRS plus WBRT, 109 GKRS plus neurosurgical resection (NSG), and 102 all three modalities. Median overall survival (mOS) was 16.6 months. mOS among patients with one versus multiple metastasis was 17.2 versus 16.0 months respectively ($p = 0.825$). For patients with one BM, mOS following GKRS alone, GKRS plus WBRT, GKRS plus NSG, and all three modalities was 9.0, 19.1, 25.5, and 25.0 months, respectively, and for patients with multiple BMs, mOS was 8.6, 20.4, 20.7, 24.5 months for the respective groups. Among all patients, multivariate analysis confirmed that tri-modality group had the longest survival (HR 0.467; 95% CI 0.350-0.623; $p < 0.001$) compared to GKRS alone; however, this was not significantly different than bi-modality approaches. Uncontrolled primary extra-CNS disease, age and KPS were also independent predictors of survival. Patients treated with GKRS plus NSG, GKRS plus WBRT, or all three modalities had improved OS versus GKRS alone. In our analysis, resection and GKRS allowed avoidance of WBRT without shortening survival.

[263] Is stereotactic radiosurgery a rational treatment option for brain metastases from small cell lung cancer? A retrospective analysis of 70 consecutive patients.

BMC cancer. 2015;15:95

Yomo S, Hayashi M

PMID: 25879433 DOI: 10.1186/s12885-015-1103-6

BACKGROUND: Because of the high likelihood of multiple brain metastases (BM) from small cell lung cancer (SCLC), the role of focal treatment using stereotactic radiosurgery (SRS) has yet to be determined. We aimed to evaluate the efficacy and limitations of upfront and salvage SRS for patients with BM from SCLC. **METHODS:** This was a retrospective and observational study analyzing 70 consecutive patients with BM from SCLC who received SRS. The median age was 68 years, and the median Karnofsky performance status (KPS) was 90. Forty-six (66%) and 24 (34%) patients underwent SRS as the upfront and salvage treatment after prophylactic or therapeutic whole brain radiotherapy (WBRT), respectively. Overall survival (OS), neurological death-free survival, remote and local tumor recurrence rates were analyzed. **RESULTS:** None of our patients were lost to follow-up and the median follow-up was 7.8 months. One-and 2-year OS rates were 43% and 15%, respectively. The median OS time was 7.8 months. One-and 2-year neurological death-free survival rates were 94% and 84%, respectively. In total, 219/292 tumors (75%) in 60 patients (86%) with sufficient radiological follow-up data were evaluated. Six-and 12-month rates of remote BM relapse were 25% and 47%, respectively. Six-and 12-month rates of local control failure were 4% and 23%, respectively. Repeat SRS, salvage WBRT and microsurgery were subsequently required in 30, 8 and one patient, respectively. Symptomatic radiation injury, treated conservatively, developed in 3 patients. **CONCLUSIONS:** The present study suggested SRS to be a potentially effective and minimally invasive treatment option for BM from SCLC either alone or after failed WBRT. Although repeat salvage treatment was needed in nearly half of patients to achieve control of distant BM, such continuation of radiotherapeutic management might contribute to reducing the rate of neurological death.

[264] Gamma knife stereotactic radiosurgery in the treatment of brainstem metastases: The MD Anderson experience.

Neuro-oncology practice. 2015;2(1):40-47

Voong KR, Farnia B, Wang Q, Luo D, McAleer MF, Rao G, Guha-Thakurta N, Likhacheva A, Ghia AJ, Brown PD, Li J
PMID: 26034640 DOI: 10.1093/nop/npu032

BACKGROUND: Brainstem metastases (BSMs) represent a significant treatment challenge. Stereotactic radiosurgery (SRS) is often used to treat BSM. We report our experience in the treatment of BSM with Gamma Knife SRS (GK_SRS).

METHODS: The records of 1962 patients with brain metastases treated with GK_SRS between 2009 and 2013 were retrospectively reviewed. Seventy-four patients with 77 BSMs and follow-up brain imaging were identified. Local control (LC), overall survival (OS), progression-free survival (PFS), and toxicity were assessed.

RESULTS: Median follow-up was 5.5 months (range, 0.2-48.5 months). Median tumor volume was 0.13 cm³ (range, 0.003-5.58 cm³). Median treatment dose was 16 Gy (range, 10-20 Gy) prescribed to 50% isodose line (range, 40%-86%). Crude LC was 94% (72/77). Kaplan-Meier estimate of median OS was 8.5 months (95% CI, 5.6-9.4 months). Symptomatic lesions and larger lesions, especially size ≥ 2 cm³, were associated with worse LC (HR = 8.70, $P = .05$; HR = 14.55, $P = .02$; HR = 62.81, $P < .001$) and worse OS (HR = 2.00, $P = .02$; HR = 2.14, $P = .03$; HR = 2.81, $P = .008$). Thirty-six percent of BSMs were symptomatic, of which 36% (10/28) resolved after SRS and 50% (14/28) had stable or improved symptoms. Actuarial median PFS was 3.9 months (95% CI, 2.7-4.9 months). Midbrain location was significant for worse PFS (HR = 2.29, $P = .03$). Toxicity was low (8%, 6/74), with size and midbrain location associated with increased toxicity (HR 1.57, $P = .05$; HR = 5.25, $P = .045$). **CONCLUSIONS:** GK_SRS is associated with high LC (94%) and low toxicity (8%) for BSMs. Presence of symptoms or lesion size ≥ 2 cm³ was predictive of worse LC and OS.

[265] Tumor resection with carmustine wafer placement as salvage therapy after local failure of radiosurgery for brain metastasis.

Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2015;22(3):561-5

Mu F, Lucas JT Jr, Watts JM, Johnson AJ, Daniel Bourland J, Laxton AW, Chan MD, Tatter SB

PMID: 25560387 DOI: 10.1016/j.jocn.2014.08.020

Prolonged survival in brain metastasis patients increases recurrence rates and places added importance on salvage therapies. Research examining carmustine polymer wafers as an adjuvant therapy for brain metastasis is limited. We present a single institution retrospective series documenting the use of BCNU wafers placed in the cavity of resected recurrent brain metastases that had failed prior stereotactic radiosurgery (SRS). Between February 2002 and April 2013, a total of 31 patients with brain metastases failed SRS and underwent resection with intracavitary placement of carmustine wafers. Clinical outcomes including local control, survival, cause of death, and toxicity were determined from electronic medical records. Kaplan-Meier analysis was performed to assess local control and survival. Imaging features were reviewed and described for patients with serial post-operative follow-up imaging examinations over time. Overall survival at 6 months and 12 months was 63% and 36%, respectively. Fourteen of 31 patients (45%) died from neurologic causes. Local control within the resection cavity was 87% and 70% at 6 and 12 months, respectively. Five patients (16%) underwent further salvage therapy following carmustine wafer placement after local failure. Resection cavities of all six patients with follow-up imaging showed linear peripheral enhancement. Pericavity and wafer enhancement was present as early as the same day as surgery and persisted in all cases to 6 months or longer. Carmustine polymer wafers are an effective salvage treatment following resection of a brain metastasis that has failed prior SRS. For patients with successful local control after wafer implantation, linear enhancement at the cavity is common.

[266] Post-treatment intracranial hemorrhage of brain metastases from hepatocellular carcinoma.

Radiation oncology journal. 2015;33(1):36-41

Kim KS, Kim K, Chie EK, Kim YJ, Yoon JH, Lee HS, Ha SW
PMID: 25874176 DOI: 10.3857/roj.2015.33.1.36

PURPOSE: To evaluate the incidence and risk factors of post-treatment intracranial hemorrhage of brain metastases from hepatocellular carcinoma (HCC). **MATERIALS AND METHODS:** Medical records of 81 patients who have been diagnosed of brain metastases from HCC and underwent surgery, radiosurgery and/or whole brain radiotherapy (WBRT) between January 2000 and December 2013 were retrospectively reviewed. **RESULTS:** Intracranial hemorrhage was present in 64 patients (79%) at the time of diagnosis. Median value of alpha-fetoprotein (AFP) level was 1,700 ng/mL. The Eastern Cooperative Oncology Group (ECOG) performance status for 20 patients was greater than 2. Fifty-seven patients underwent WBRT and the others were treated with surgery and/or radiosurgery without WBRT. During follow-up, 12 events of intracranial hemorrhage after treatment were identified. Three-month post-treatment hemorrhage rate was 16.1%. Multivariate analyses revealed that ECOG performance status, AFP, and WBRT were associated with post-treatment hemorrhage ($p = 0.013, 0.013, \text{ and } 0.003$, respectively). Kaplan-Meier analysis showed that 3-month post-treatment hemorrhage rate of new lesion was higher in patients treated without WBRT, although statistical significance was not reached. (18.6% vs. 4.6%; $p = 0.104$). Ten of 12 patients with post-treatment hemorrhage died with neurologic cause. **CONCLUSION:** WBRT should be considered to prevent post-treatment hemorrhage in the treatment of brain metastases from HCC.

[267] Local control of brain metastasis: treatment outcome of focal brain treatments in relation to subtypes.

Journal of breast cancer. 2015;18(1):29-35

Chong JU, Ahn SG, Lee HM, Park JT, Lee SA, Park S, Jeong J, Kim SI
PMID: 25834608 DOI: 10.4048/jbc.2015.18.1.29

PURPOSE: To investigate treatment options for local control of metastasis in the brain, we compared focal brain treatment (FBT) with or without whole brain radiotherapy (WBRT) vs. WBRT alone, for breast cancer patients with tumor relapse in the brain. We also evaluated treatment outcomes according to the subtypes. **METHODS:** We conducted a retrospective review of breast cancer patients with brain metastasis after primary surgery. All patients received at least one local treatment for brain metastasis. Surgery or stereotactic radiosurgery was categorized as FBT. Patients were divided into two groups: the FBT group received FBT+/-WBRT, whereas the non-FBT group received WBRT alone. Subtypes were defined as follows: hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative, HR-positive/HER2-positive, HR-negative/HER2-positive, and triple-negative (TN). We examined the overall survival after brain metastasis (OSBM), brain metastasis-specific survival (BMSS), and brain metastasis-specific progression-free survival (BMPFS). **RESULTS:** A total of 116 patients were identified. After a median follow-up of 50.9 months, the median OSBM was 11.5 months (95% confidence interval, 9.0-14.1 months). The FBT group showed significantly superior OSBM and BMSS. However, FBT was not an independent prognostic factor for OSBM and BMSS on multivariate analyses. In contrast, multivariate analyses showed that patients who underwent surgery had improved BMPFS, indicating local control of metastasis in the brain. FBT resulted in better BMPFS in patients with HR-negative/HER2-positive cancer or the TN subtype. **CONCLUSION:** We found that patients who underwent surgery experienced improved local control of brain metastasis, regardless of its extent. Furthermore, FBT showed positive results and could be considered for better local control of brain metastasis in patients with aggressive subtypes such as HER2-positive and TN.

[268] Gamma knife radiosurgery for elderly patients with brain metastases: evaluation of scoring systems that predict survival.

BMC cancer. 2015;15:54

Park JY, Moon KS, Lee KH, Lim SH, Jang WY, Lee H, Jung TY, Kim IY, Jung S
PMID: 25885321 DOI: 10.1186/s12885-015-1070-y

BACKGROUND: Gamma knife radiosurgery (GKRS) has been increasingly employed for the treatment of elderly patients with brain metastases, mainly due to its demonstrated effectiveness and low complication rate. However, only a few studies have investigated the prognostic factors that influence the survival of elderly patients after GKRS. The purpose of this study was to identify a scoring system that is able to predict the survival of elderly patients undergoing GKRS using data obtained at the time of diagnosis for brain metastases. **METHODS:** Between 2004 and 2011, death was confirmed in 147 patients aged 70 years and older who had been treated with GKRS for brain metastases. Median age at the time of GKRS was 75.7 years (range, 70-86 years). The median tumor volume was 5.1 cm³ (range, 0.05-59.9 cm³). The median marginal prescription dose was 21.4 Gy (range, 14-25 Gy). **RESULTS:** The median survival was 167 days. Overall survival rates at 6 months and 1 year were 60.4% and 29.4%, respectively. Among the patient characteristics pertaining to systemic cancer and brain metastasis for which data were obtained preoperatively, a multivariate analysis showed that low Karnofsky performance status (KPS ≤ 80 , $P = 0.047$) and the presence of extracranial metastases ($P = 0.014$) detected at the time of brain metastasis diagnosis were independent prognostic factors for short survival. A high score index for radiosurgery (SIR score ≥ 4 , $P = 0.024$) and a high graded prognostic assessment (GPA score ≥ 2 , $P = 0.004$) were associated with longer survival. A multivariate analysis of the important characteristics of systemic cancer, and the scoring system evaluating survival duration showed that a low GPA score was the most powerful independent factor for predicting short survival (hazard ratio 1.756, 95% confidence interval 1.252-2.456, $P = 0.001$). **CONCLUSIONS:** GKRS is a safe approach to treat brain metastases in patients age 70 years and older. In this group, our study identified GPA score at the time of GKRS as a powerful prognostic factor for survival.

[269] Elucidating the role of incidental use of beta-blockers in patients with metastatic brain tumors in controlling tumor progression and survivability.

Neurology India. 2015;63(1):19-23

Bir SC, Kalakoti P, Ahmed O, Bollam P, Nanda A
PMID: 25751464 DOI: 10.4103/0028-3886.152625

BACKGROUND: Beta-adrenergic antagonists have demonstrated beneficial effects in tumor progression and survivability in patients with various cancers by inhibiting norepinephrine-induced tumor cell migration. However, little is known about their effects on the outcomes of metastatic brain tumors (MBTs). This study was undertaken to evaluate the effects of beta-blockers, if any, on the outcome of MBTs, and their possible role in controlling tumor progression and survivability. **MATERIALS AND METHODS:** A retrospective cohort analysis of 225 patients identified as having MBTs presenting to our institution from 2001 through 2013 was conducted by reviewing electronic patient records. Patients were categorized into three groups: Group A comprised hypertensives on beta-blockers only (40, 18%), Group B comprised hypertensive patients on antihypertensive medications other than beta-agonists (65, 29%), and Group C comprised normotensives (120, 53%). All outcomes were compared using the data on pre- and post-gamma knife radiosurgery (GKRS) for these groups. One-way analysis of variance (ANOVA) was used to compare the radiological and clinical outcomes in the patient population following beta-blockers usage in Group A versus groups B and C. Cox regression model was used to demonstrate prognostic factors for the outcome in patients having different primaries. Overall survival period was plotted on Kaplan-Meier curves. The log-rank (Mantel-Cox) test was used to analyze the survival difference in the cases. $P < 0.05$ was considered significant. **RESULTS:** The mean age of patients was 57.34 \pm 10.98 years (range: 30-87 years) and 44% were males. More than half (130/225, 58%) of patients with MBT had their primary tumor source in the lung, 16% in the breast, and 7% each in the kidneys and the

rectum. Frontal lobe was the most commonly affected (80, 35.5%). Statistically significant control of tumor growth ($P = 0.001$), tumor progression ($P = 0.0001$), and higher survival outcomes ($P = 0.015$) were observed in Group A as compared to other groups. In comparing the different groups, breast primaries showed the strongest correlation to survival benefit ($P = 0.049$) from beta-blocker usage as a primary antihypertensive medication. **CONCLUSION:** Concomitant use of beta-blockers with conventional therapy may offer potential benefit to hypertensive patients developing MBTs by ameliorating tumor progression and conferring a survival advantage. This effect was most notable in patients with primary tumors originating in the breast. Prospective studies, molecular research, and randomized controlled trials are warranted to further explore this promising effect.

[270] Survival of melanoma patients with brain metastases treated with ipilimumab and stereotactic radiosurgery.

Cancer medicine. 2015;4(1):1-6

Tazi K, Hathaway A, Chiuzan C, Shirai K
PMID: 25164960 DOI: 10.1002/cam4.315

UNLABELLED: Historically, melanoma with brain metastases has a poor prognosis. In this retrospective medical record review, we report the outcome of patients with stage IV melanoma with brain metastases treated with ipilimumab and brain stereotactic radiosurgery (SRS). All patients with metastatic melanoma treated with ipilimumab from June 2010 to September 2012 were identified and stratified by presence (A) or absence (B) of brain metastases at the time of ipilimumab administration. All patients with brain metastases received SRS. Overall survival (OS) was defined as time from the date of stage IV diagnosis and the time of ipilimumab administration to death or last follow-up. Survival curves were estimated using the Kaplan-Meier method, and Cox proportional hazards model was employed to compute the hazard ratios (HR). **RESULTS:** Five out of 10 patients in Cohort A and 10 out of 21 patients in Cohort B died as of last follow-up. In Cohort A, median number of lesions treated with SRS was 3. Median survivals from date of stage IV for Cohorts A and B were 29.3 and 33.1 months, respectively ($HR = 0.93$, $P = 0.896$). Median survival from cycle 1 ipilimumab was 16.5 and 24.5 months for Cohort A and B, respectively ($HR = 1.05$, $P = 0.931$). The 3-year survival rates from the date of cycle one of ipilimumab administration for Cohort A and B were 50% (95% CI: 27-93%) and 39% (95% CI: 19-81%), respectively. Eight of 10 patients in Cohort A maintained a good PS. Survival of patients with melanoma brain metastases treated with ipilimumab combined with SRS may be comparable to patients without brain metastases.

2014

[271] Long term outcome of Gamma Knife radiosurgery for metastatic brain tumors.

Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2014;21(12):2122-8

Bir SC, Ambekar S, Nanda A

PMID: 25065951 DOI: 10.1016/j.jocn.2014.05.015

Gamma Knife radiosurgery (GKRS; Elekta AB, Stockholm, Sweden) has emerged as an important treatment option for metastatic brain tumors (MBT). However, the long term outcome of GKRS on MBT is not well understood. We reviewed the treatment of MBT with GKRS at our institution. We performed a retrospective review (2000-2013) of 298 patients with MBT who received GKRS. The study population was monitored clinically and radiographically after GKRS treatment. Survival benefits and predictive factors of the outcome were analyzed using the Kaplan-Meier test and Cox regression model, respectively. GKRS in MBT showed significant variation in tumor growth control (decreased in 135 [45%] patients, arrested growth in 91 [37%] patients and increased tumor size in 72 [24%] patients). The median survival in the study population was 17 months. Overall

and progression free survival after 3 years were 25% and 45%, respectively. The predictive factors for improving survival in the patients with MBT were recursive partitioning analysis class I ($p < 0.0001$), absence of hydrocephalus ($p < 0.0001$), Karnofsky Performance Status (KPS) > 80 ($p = 0.007$) and absence of recurrent MBT ($p = 0.01$). Forty (12%), 15 (4.3%) and two (0.6%) patients required GKRS, resection and whole brain radiation, respectively, after initial GKRS due to tumor progression and worsening of signs and symptoms. Our findings revealed that GKRS offers a high rate of tumor control and good survival benefits in both new and recurrent patients with MBT. Thus, GKRS is an effective treatment option for new patients with MBT, as well as an adjuvant therapy in patients with recurrent MBT.

[272] Quantifying and improving the efficiency of Gamma Knife treatment plans for brain metastases: results of a 1-year audit.

Journal of neurosurgery. 2014;121 Suppl:44-50

Wright G, Hatfield P, Loughrey C, Reiner B, Bownes P

PMID: 25434936 DOI: 10.3171/2014.7.GKS141415

OBJECT: A method for quantifying the efficiency of Gamma Knife treatment plans for metastases was previously implemented by the authors to retrospectively identify the least efficient plans and has provided insights into improved planning strategies. The aim of the current work was to ascertain whether those insights led to improved treatment plans. **METHODS:** Following completion of the initial study, a 1-year audit of metastasis plans created at St. James's Institute of Oncology was carried out. Audited recent plans were compared with the earlier plans of the initial study, in terms of their efficiency and dosimetric quality. The statistical significance of any differences between relevant plan parameters was quantified by Mann-Whitney U-tests. Comparisons were made between all plans and repeated for a reduced set of plans from which the smallest lesions treated with a single 4-mm shot were excluded. The plan parameters compared were a plan efficiency index (PEI), the number of shots, Paddick conformity index (PCI), gradient index (GI), and percent coverage (of the lesion by the prescription isodose). **RESULTS:** A total of 157 metastatic lesions were included in the audit and were compared with 241 in the initial study. In a comparison of all cases, the audited plans achieved a higher median PEI score than did the earlier plans from the initial study (1.08 vs 1.02), indicating improved efficiency of the audited plans. When the smallest lesions (for which there was little scope for varying plan strategy) were discounted, the improvement in median PEI score was greater (1.23 vs 1.03, $p < 0.001$). This improvement in efficiency corresponds to an estimated mean (maximum) time saving of 15% (66%) per lesion (11 minutes [64 minutes] on the day of treatment). The modified planning strategy yielding these efficiency improvements did not rely on the use of significantly fewer shots (median 11 vs 11 shots, $p = 0.924$), nor did it result in significant detriment to dosimetric quality (median coverage 99% vs 99%, median PCI 0.84 vs 0.83, $p = 0.449$, and median GI 2.72 vs 2.67, $p = 0.701$, audited plans vs initial plans, respectively).

CONCLUSIONS: Choice of planning strategy can substantially affect plan efficiency and thus strongly influence treatment time. Through increased emphasis on efficiency, resulting from the introduction of PEI combined with a modified planning strategy informed by previous work, it has been possible to reduce times for metastatic plans without compromising their dosimetric quality. Although the average time savings achieved per lesion are moderate, the potential benefits per patient are greater for those with multiple metastases. Reducing treatment times has clear benefits with regard to patient comfort and throughput. In addition, optimization of plan efficiency may potentially affect the biologically effective dose from Gamma Knife treatments and offers opportunity for further work.

[273] Stereotactic radiosurgery for patients with multiple brain metastases: a case-matched study comparing treatment results for patients with 2-9 versus 10 or more tumors.

Journal of neurosurgery. 2014;121 Suppl:16-25

Yamamoto M, Kawabe T, Sato Y, Higuchi Y, Nariai T, Watanabe S, Kasuya H
PMID: 25434933 DOI: 10.3171/2014.8.GKS141421

OBJECT: Although stereotactic radiosurgery (SRS) alone is not a standard treatment for patients with 4-5 tumors or more, a recent trend has been for patients with 5 or more, or even 10 or more, tumors to undergo SRS alone. The aim of this study was to reappraise whether the treatment results for SRS alone for patients with 10 or more tumors differ from those for patients with 2-9 tumors.

METHODS: This was an institutional review board-approved, retrospective cohort study that gathered data from the Katsuta Hospital Mito GammaHouse prospectively accumulated database. Data were collected for 2553 patients who consecutively had undergone Gamma Knife SRS alone, without whole-brain radiotherapy (WBRT), for newly diagnosed (mostly) or recurrent (uncommonly) brain metastases during 1998-2011. Of these 2553 patients, 739 (28.9%) with a single tumor were excluded, leaving 1814 with multiple metastases in the study. These 1814 patients were divided into 2 groups: those with 2-9 tumors (Group A, 1254 patients) and those with 10 or more tumors (Group B, 560 patients). Because of considerable bias in pre-SRS clinical factors between groups A and B, a case-matched study, which used the propensity score matching method, was conducted for clinical factors (i.e., age, sex, primary tumor state, extracerebral metastases, Karnofsky Performance Status, neurological symptoms, prior procedures [surgery and WBRT], volume of the largest tumor, and peripheral doses). Ultimately, 720 patients (360 in each group) were selected. The standard Kaplan-Meier method was used to determine post-SRS survival times and post-SRS neurological death-free survival times. Competing risk analysis was applied to estimate cumulative incidence for local recurrence, repeat SRS for new lesions, neurological deterioration, and SRS-induced complications. **RESULTS:** Post-SRS median survival times did not differ significantly between the 2 groups (6.8 months for Group A vs 6.0 months for Group B; hazard ratio [HR] 1.133, 95% CI 0.974-1.319, $p = 0.10$). Furthermore, rates of neurological death were very similar: 10.0% for group A and 9.4% for group B ($p = 0.89$); neurological death-free survival times did not differ significantly between the 2 groups (HR 1.073, 95% CI 0.649-1.771, $p = 0.78$). The cumulative incidence of local recurrence (HR 0.425, 95% CI 0.0181-0.990, $p = 0.04$) and repeat SRS for new lesions (HR 0.732, 95% CI 0.554-0.870, $p = 0.03$) were significantly lower for Group B than for Group A patients. No significant differences between the groups were found for cumulative incidence for neurological deterioration (HR 0.994, 95% CI 0.607-1.469, $p = 0.80$) or SRS-related complications (HR 0.541, 95% CI 0.138-2.112, $p = 0.38$). **CONCLUSIONS:** Post-SRS treatment results (i.e., median survival time; neurological death-free survival times; and cumulative incidence for local recurrence, repeat SRS for new lesions, neurological deterioration, and SRS-related complications) were not inferior (neither less effective nor less safe) for patients in Group B than for those in Group A. We conclude that carefully selected patients with 10 or more tumors are not unfavorable candidates for SRS alone. A randomized controlled trial should be conducted to test this hypothesis.

[274] Gamma Knife surgery for treating brain metastases arising from hepatocellular carcinomas.

Journal of neurosurgery. 2014;121 Suppl:102-9

Park ES, Kwon DH, Park JB, Lee DH, Cho YH, Kim JH, Kim CJ
PMID: 25434943 DOI: 10.3171/2014.7.GKS141507

OBJECT: Brain metastases from hepatocellular carcinoma (HCC) are rare, and the evidence of the effectiveness of Gamma Knife surgery (GKS) in this disease is lacking. The authors report their institutional experience with GKS in patients with brain metastases from HCCs. **METHODS:** The authors retrospectively reviewed the medical records of 73 consecutive patients who had a combined total of 141 brain metastases arising from HCCs and were treated with GKS. Sixty-four (87.7%) patients were male, and the mean age of the patients was 52.5 years (range 30-79 years). The mean tumor volume was 7.35 cm³ (range 0.19-33.7 cm³). The median margin dose prescribed was 23 Gy (range 15-32 Gy). Univariate and multivariate survival analyses were performed to identify possible prognostic factors of outcomes. **RESULTS:** The estimated rate of local tumor control was 79.6% at 3 months after GKS. The median overall survival time after GKS was 16 weeks. The actuarial survival rates were 76.7%, 58.9%, and 26.0% at

4, 12, and 24 weeks after GKS, respectively. In the univariate analysis, an age of ≤ 65 years, Child-Pugh Class A (pertaining to liver function), high Karnofsky Performance Scale score (≥ 70), and low Radiation Therapy Oncology Group recursive partitioning analysis class (I or II) were positively associated with the survival times of patients. No statistically significant variable was identified in the multivariate analysis. **CONCLUSIONS:** Although survival was extremely poor in patients with brain metastases from HCCs, GKS showed acceptable local tumor control at 3 months after the treatment. The authors suggest that GKS represents a noninvasive approach that may provide a valuable option for treating patients with brain metastases from HCCs.

[275] Stereotactic radiosurgery to the resection bed for intracranial metastases and risk of leptomeningeal carcinomatosis.

Journal of neurosurgery. 2014;121 Suppl:75-83

Ojerholm E, Lee JY, Thawani JP, Miller D, O'Rourke DM, Dorsey JF, Geiger GA, Nagda S, Kolker JD, Lustig RA, Alonso-Basanta M
PMID: 25434940 DOI: 10.3171/2014.6.GKS14708

OBJECT: Following resection of a brain metastasis, stereotactic radiosurgery (SRS) to the cavity is an emerging alternative to postoperative whole-brain radiation therapy (WBRT). This approach attempts to achieve local control without the neurocognitive risks associated with WBRT. The authors aimed to report the outcomes of a large patient cohort treated with this strategy. **METHODS:** A retrospective review identified 91 patients without a history of WBRT who received Gamma Knife (GK) SRS to 96 metastasis resection cavities between 2007 and 2013. Patterns of intracranial control were examined in the 86 cases with post-GK imaging. Survival, local failure, and distant failure were estimated by the Kaplan-Meier method. Prognostic factors were tested by univariate (log-rank test) and multivariate (Cox proportional hazards model) analyses. **RESULTS:** Common primary tumors were non-small cell lung (43%), melanoma (14%), and breast (13%). The cases were predominantly recursive partitioning analysis Class I (25%) or II (70%). Median preoperative metastasis diameter was 2.8 cm, and 82% of patients underwent gross-total resection. A median dose of 16 Gy was delivered to the 50% isodose line, encompassing a median treatment volume of 9.2 cm³. Synchronous intact metastases were treated in addition to the resection bed in 43% of cases. Patients survived a median of 22.3 months from the time of GK. Local failure developed in 16 cavities, for a crude rate of 18% and 1-year actuarial local control of 81%. Preoperative metastasis diameter ≥ 3 cm and residual or recurrent tumor at the time of GK were associated with local failure ($p = 0.04$ and 0.008, respectively). Distant intracranial failure occurred in 55 cases (64%) at a median of 7.3 months from GK. Salvage therapies included WBRT and additional SRS in 33% and 31% of patients, respectively. Leptomeningeal carcinomatosis developed in 12 cases (14%) and was associated with breast histology and infratentorial cavities ($p = 0.024$ and 0.012, respectively). **CONCLUSIONS:** This study bolsters the existing evidence for SRS to the resection bed. Local control rates are high, but patients with larger preoperative metastases or residual/recurrent tumor at the time of SRS are more likely to fail at the cavity. While most patients develop distant intracranial failure, an SRS approach spared or delayed WBRT in the majority of cases. The risk of leptomeningeal carcinomatosis does not appear to be elevated with this strategy.

[276] Early Gamma Knife stereotactic radiosurgery to the tumor bed of resected brain metastasis for improved local control.

Journal of neurosurgery. 2014;121 Suppl:69-74

Iorio-Morin C, Masson-Cote L, Ezahr Y, Blanchard J, Ebacher A, Mathieu D
PMID: 25434939 DOI: 10.3171/2014.7.GKS141488

OBJECT: Optimal case management after surgical removal of brain metastasis remains controversial. Although postoperative whole-brain radiation therapy (WBRT) has been shown to prevent local recurrence and decrease deaths, this modality can substantially decrease neurocognitive function and quality of life. Stereotactic radiosurgery (SRS) can theoretically achieve the same level of local control with fewer side effects, although studies conclusively demonstrating such

outcomes are lacking. To assess the effectiveness and safety profile of tumor bed SRS after resection of brain metastasis, the authors performed a retrospective analysis of 110 patients who had received such treatment at the Centre Hospitalier Universitaire de Sherbrooke. They designed the study to identify risk factors for local recurrence and placed special emphasis on factors that could potentially be addressed. **METHODS:** Patients who had received treatment from 2004 through 2013 were included if they had undergone surgical removal of 1 or more brain metastases and if the tumor bed was treated by SRS regardless of the extent of resection or prior WBRT. All cases were retrospectively analyzed for patient and tumor-specific factors, treatment protocol, adverse outcomes, cavity outcomes, and survival for as long as follow-up was available. Univariate and multivariate Cox regression analyses were performed to identify risk factors for local recurrence and predictors of increased survival times. **RESULTS:** Median patient age at first SRS treatment was 58 years (range 37-84 years). The most frequently diagnosed primary tumor was non-small cell lung cancer. The rate of gross-total resection was 81%. The median Karnofsky Performance Scale score was 90%. Tumor bed SRS was performed at a median of 3 weeks after surgery. Median follow-up and survival times were 10 and 11 months, respectively. Actuarial local control of the cavity at 12 months was 73%; median time to recurrence was 6 months. According to multivariate analysis, risk factors for recurrence were a longer surgery-to-SRS delay (HR 1.625, $p = 0.003$) and a lower maximum radiation dose delivered to the cavity (HR 0.817, $p = 0.006$). Factors not associated with increased recurrence were subtotal or piecemeal resections, prior WBRT, histology of the primary tumor, and larger cavity volume. No factors predictive of survival were identified. Symptomatic radiation-induced enhancement occurred in 6% of patients and leptomeningeal dissemination in 11%. Pathologically confirmed radiation-induced necrosis occurred in 1 (0.9%) patient. **CONCLUSIONS:** Adjuvant tumor bed SRS after the resection of brain metastasis is a valuable alternative to adjuvant WBRT. Risk factors for local recurrence are lower maximum radiation dose and a surgery-to-SRS delay longer than 3 weeks. Outcomes were not worse for patients who had undergone prior WBRT and subtotal or piecemeal resections. Pending the results of prospective randomized controlled trials, the authors' study supports the safety and efficacy of adjuvant SRS after resection of brain metastasis. SRS should be performed as early as possible, ideally within 3 weeks of the surgery.

[277] Cost-effectiveness of stereotactic radiosurgery with and without whole-brain radiotherapy for the treatment of newly diagnosed brain metastases.

Journal of neurosurgery. 2014;121 Suppl:84-90
Hall MD, McGee JL, McGee MC, Hall KA, Neils DM, Klopfenstein JD, Elwood PW
PMID: 25434941 DOI: 10.3171/2014.7.GKS14972

OBJECT: Stereotactic radiosurgery (SRS) alone is increasingly used in patients with newly diagnosed brain metastases. Stereotactic radiosurgery used together with whole-brain radiotherapy (WBRT) reduces intracranial failure rates, but this combination also causes greater neurocognitive toxicity and does not improve survival. Critics of SRS alone contend that deferring WBRT results in an increased need for salvage therapy and in higher costs. The authors compared the cost-effectiveness of treatment with SRS alone, SRS and WBRT (SRS+WBRT), and surgery followed by SRS (S+SRS) at the authors' institution. **METHODS:** The authors retrospectively reviewed the medical records of 289 patients in whom brain metastases were newly diagnosed and who were treated between May 2001 and December 2007. Overall survival curves were plotted using the Kaplan-Meier method. Multivariate proportional hazards analysis (MVA) was used to identify factors associated with overall survival. Survival data were complete for 96.2% of patients, and comprehensive data on the resource use for imaging, hospitalizations, and salvage therapies were available from the medical records. Treatment costs included the cost of initial and all salvage therapies for brain metastases, hospitalizations, management of complications, and imaging. They were computed on the basis of the 2007 Medicare fee schedule from a payer perspective. Average treatment cost and average cost per month of median survival were compared. Sensitivity analysis was performed to examine the impact of variations in key cost variables. **RESULTS:** No significant differences in overall

survival were observed among patients treated with SRS alone, SRS+WBRT, or S+SRS with respective median survival of 9.8, 7.4, and 10.6 months. The MVA detected a significant association of overall survival with female sex, Karnofsky Performance Scale (KPS) score, primary tumor control, absence of extracranial metastases, and number of brain metastases. Salvage therapy was required in 43% of SRS-alone and 26% of SRS+WBRT patients ($p < 0.009$). Despite an increased need for salvage therapy, the average cost per month of median survival was \$2412 per month for SRS alone, \$3220 per month for SRS+WBRT, and \$4360 per month for S+SRS ($p < 0.03$). Compared with SRS+WBRT, SRS alone had an average incremental cost savings of \$110 per patient. Sensitivity analysis confirmed that the average treatment cost of SRS alone remained less than or was comparable to SRS+WBRT over a wide range of costs and treatment efficacies. **CONCLUSIONS:** Despite an increased need for salvage therapy, patients with newly diagnosed brain metastases treated with SRS alone have similar overall survival and receive more cost-effective care than those treated with SRS+WBRT. Compared with SRS+WBRT, initial management with SRS alone does not result in a higher average cost.

[278] Stereotactic radiosurgery for intraventricular brain metastases.

Journal of neurosurgery. 2014;121 Suppl:26-34
Farnia B, Voong KR, Brown PD, Allen PK, Guha-Thakurta N, Prabhu SS, Rao G, Wang Q, Zhao Z, Mahajan A
PMID: 25434934 DOI: 10.3171/2014.8.GKS141354

OBJECT: The authors' institution previously reported a 69% rate of crude local control for surgical management of lateral ventricle metastases at the University of Texas MD Anderson Cancer Center. For comparison, the authors here report their institutional experience with use of stereotactic radiosurgery (SRS) to treat intraventricular metastases. **METHODS:** To identify patients with intraventricular metastases for this retrospective review, the authors queried an institutional SRS database containing the medical records of 1962 patients with 5800 brain metastases who consecutively underwent SRS from June 2009 through October 2013. End points assessed were local control (crude and locoregional), distant failure-free survival, progression-free survival, and overall survival. **RESULTS:** Of the 1962 records examined, those for 25 (1.3%) patients with 30 (0.52%) intraventricular metastases were identified. Median patient age at SRS was 55.8 years. The most common primary malignancy was renal cell carcinoma ($n = 13$), followed by melanoma ($n = 7$) and breast adenocarcinoma ($n = 5$). Median tumor volume was 0.75 cm³ (range 0.01-5.6 cm³). Most lesions were located in the lateral ventricles ($n = 25$, 83.3%) and were treated to a median dose of 20 Gy (range 14-20 Gy). A total of 12 (48%) patients received whole-brain radiation therapy, most ($n = 10$) before SRS. With a median follow-up of 11.4 months (range 1.6-39.2 months), the rate of crude local control was 93.3%, and the rates of 6-month and 1-year actuarial locoregional control were 85.2% and 56.2%, respectively. The median overall survival time after SRS was 11.6 months (range 1.3-38.9 months), and the 6-month and 1-year actuarial rates were 87.1% and 46.7%, respectively. Disease dissemination developed in 7 (28%) patients as a second intraventricular metastatic lesion ($n = 3$, 12%), leptomeningeal disease ($n = 3$, 12%), or both ($n = 1$, 4%). Radiographic changes developed in 5 (20%) patients and included necrosis ($n = 2$, 8%) and hemorrhage ($n = 3$, 12%). A primary diagnosis of renal cell carcinoma was associated with an improved rate of distant failure-free survival ($p = 0.05$) and progression-free survival ($p = 0.08$). **CONCLUSIONS:** SRS provides excellent local control for intraventricular metastases, with acceptable treatment-related toxicity, thereby supporting nonsurgical treatment for these lesions. The propensity for intraventricular dissemination among intraventricular metastases seems to be histologically dependent.

[279] A new grading system focusing on neurological outcomes for brain metastases treated with stereotactic radiosurgery: the modified Basic Score for Brain Metastases.

Journal of neurosurgery. 2014;121 Suppl:35-43

Serizawa T, Higuchi Y, Nagano O, Matsuda S, Ono J, Saeki N, Hirai T, Miyakawa A, Shibamoto Y

PMID: 25434935 DOI: 10.3171/2014.7.GKS14980

OBJECT: The Basic Score for Brain Metastases (BSBM) proposed by Lorenzoni and colleagues is one of the best grading systems for predicting survival periods after stereotactic radiosurgery (SRS) for brain metastases. However, it includes no brain factors and cannot predict neurological outcomes, such as preservation of neurological function and prevention of neurological death. Herein, the authors propose a modified BSBM, adding 4 brain factors to the original BSBM, enabling prediction of neurological outcomes, as well as of overall survival, in patients undergoing SRS. **METHODS:** To serve as neurological prognostic scores (NPSs), the authors scored 4 significant brain factors for both preservation of neurological function (qualitative survival) and prevention of neurological death (neurological survival) as 0 or 1 as described in the following: > 10 brain tumors = 0 or <= 10 = 1, total tumor volume > 15 cm(3) = 0 or <= 15 cm(3) = 1, MRI findings of localized meningeal dissemination (yes = 0 or no = 1), and neurological symptoms (yes = 0 or no = 1). According to the sum of NPSs, patients were classified into 2 subgroups: Subgroup A with a total NPS of 3 or 4 and Subgroup B with an NPS of 0, 1, or 2. The authors defined the modified BSBM according to the NPS subgroup classification applied to the original BSBM groups. The validity of this modified BSBM in 2838 consecutive patients with brain metastases treated with SRS was verified. **RESULTS:** Patients included 1868 with cancer of the lung (including 1604 with non-small cell lung cancer), 355 of the gastrointestinal tract, 305 of the breast, 176 of the urogenital tract, and 134 with other cancers. Subgroup A had 2089 patients and Subgroup B 749. Median overall survival times were 2.6 months in BSBM 0 (382 patients), 5.7 in BSBM 1 (1143), 11.4 in BSBM 2 (1011) and 21.7 in BSBM 3 (302), and pairwise differences between the BSBM groups were statistically significant (all $p < 0.0001$). One-year qualitative survival rates were 64.6% (modified BSBM 0A, 204 patients), 45.0% (0B, 178), 82.5% (1A, 825), 63.3% (1B, 318), 86.4% (2A, 792), 73.7% (2B, 219), 91.4% (3A, 268), and 73.5% (3B, 34). One-year neurological survival rates were 82.6% (0A), 52.4% (0B), 90.5% (1A), 78.1% (1B), 91.1% (2A), 83.2% (2B), 93.9% (3A), and 76.3% (3B), where A and B identify the subgroup. Statistically significant differences in both qualitative and neurological survivals between Subgroups A and B were detected in all BSBM groups. **CONCLUSIONS:** The authors' new index, the modified BSBM, was found to be excellent for predicting neurological outcomes, independently of life expectancy, in SRS-treated patients with brain metastases.

[280] Predictors of survival, neurologic death, local failure, and distant failure after gamma knife radiosurgery for melanoma brain metastases.

World neurosurgery. 2014;82(6):1250-5

Neal MT, Chan MD, Lucas JT Jr, Loganathan A, Dillingham C, Pan E, Stewart JH 4th, Bourland JD, Shaw EG, Tatter SB, Ellis TL

PMID: 23402867 DOI: 10.1016/j.wneu.2013.02.025

OBJECTIVE: This study sought to assess clinical outcomes in patients receiving gamma knife radiosurgery (GK) for treatment of brain metastases from melanoma and evaluate for potential predictive factors. **METHODS:** We reviewed 188 GK procedures in 129 consecutive patients that were treated for brain metastases from melanoma. The population consisted of 84 males and 45 females with a median age of 57 years. Fifty-five patients (43%) had a single metastasis. Seventy-one patients (55%) received chemotherapy, 58 patients (45%) received biologic agents, and 36 patients (28%) received prior whole brain radiation therapy (WBRT). The median marginal dose was 18.8 Gy (range 12 to 24 Gy). **RESULTS:** Actuarial survival was 52%, 26%, and 13% at 6, 12, and 24 months, respectively. The median survival time was 6.7 months. Local tumor control was 95%, 81% 53% at 6, 12, and 24 months, respectively. The median time to LBF was 25.2 months. Freedom from distant brain failure was 40%, 29%, and 10% at 6, 12, and 24 months, and the median time to DBF was 4.6 months. At the time of data analysis, 108 patients (84%) had died. Fifty-eight patients (52%) died from neurologic death. The median time to neurologic death from GK treatment was 7.9 months. Multivariate analysis revealed that hemorrhage of metastases prior to GK ($P = .02$) and LBF (P

= .03) were the dominant predictors of neurologic death. **CONCLUSIONS:** GK achieves excellent local control and may improve outcomes as a component of a multidisciplinary treatment strategy. Distant brain failure and neurologic demise remain problematic and prospective trials are necessary.

[281] Validity of prognostic grading indices for brain metastasis patients undergoing repeat radiosurgery.

World neurosurgery. 2014;82(6):1242-9

Yamamoto M, Kawabe T, Higuchi Y, Sato Y, Nariai T, Watanabe S, Barford BE, Kasuya H

PMID: 25109592 DOI: 10.1016/j.wneu.2014.08.008

OBJECTIVES: We tested the validity of 5 prognostic indices, Recursive Partitioning Analysis (RPA), Score Index for Radiosurgery (SIR), Basic Score for Brain Metastases (BSBM), Graded Prognostic Assessment (GPA), and Modified-RPA, for patients who underwent repeat stereotactic radiosurgery (re-SRS).

METHODS: For this study, we used our database, which included 804 patients who underwent gamma knife re-SRS during the period 1998-2013. **RESULTS:** There were statistically significant survival differences among patients stratified into 3 or 4 groups based on the 5 systems ($P < 0.001$). With RPA, SIR, BSBM, and the Modified-RPA, there were statistically significant median survival time (MST) differences between any 2 pairs within the 3/4 groups. With the GPA system, however, the MST difference between the GPA 3.5-4.0 and GPA 3.0 groups did not reach statistical significance ($P = 0.48$). There were large patient number discrepancies among the 3/4 groups in the RPA, SIR, BSBM, and GPA whereas patient numbers were very similar among the 3 Modified-RPA system groups. Our present results show the RPA and BSBM systems to reflect changes less well, with 86%-95% of patients remaining in the same categories between the first and second SRS procedures. However, with SIR, GPA, and the Modified-RPA, 25%-31% of patients were categorized into different subclasses, either better or worse. With the modified-RPA system, such categorical change correlated well with post-re-SRS MSTs. **CONCLUSIONS:** Among the 5 systems, based on patient number proportions, MST separation among the 3/4 groups, and/or detailed reflection of status changes, the Modified-RPA system was shown to be most applicable to re-SRS patients.

[282] Utility of intravoxel incoherent motion MR imaging for distinguishing recurrent metastatic tumor from treatment effect following gamma knife radiosurgery: initial experience.

AJNR. American journal of neuroradiology. 2014;35(11):2082-90

Kim DY, Kim HS, Goh MJ, Choi CG, Kim SJ

PMID: 24970548 DOI: 10.3174/ajnr.A3995

BACKGROUND AND PURPOSE: Intravoxel incoherent motion MR imaging can simultaneously measure the diffusion and perfusion characteristics of brain tumors. Our aim was to determine the utility of intravoxel incoherent motion-derived perfusion and diffusion parameters for assessing the treatment response of metastatic brain tumor following gamma knife radiosurgery. **MATERIALS AND METHODS:** Ninety-one consecutive patients with metastatic brain tumor treated with gamma knife radiosurgery were assessed by using intravoxel incoherent motion imaging. Two readers independently calculated the 90th percentile and the 10th percentile histogram cutoffs for perfusion, normalized CBV, diffusion, and ADC. Areas under the receiver operating characteristic curve and interreader agreement were assessed. **RESULTS:** With the combination of the 90th percentile histogram cutoff for perfusion and the 10th percentile histogram cutoff for diffusion, the sensitivity and specificity for differentiating recurrent tumor and treatment were 79.5% and 92.3% for reader 1 and 84.6% and 94.2% for reader 2, respectively. With the combination of the 90th percentile histogram cutoff for normalized CBV and the 10th percentile histogram cutoff for ADC, the sensitivity and specificity for differentiating recurrent tumor and treatment were 69.2% and 100.0% for reader 1 and 74.3% and 100.0% for reader 2, respectively. Compared with the combination of 90th percentile histogram cutoff for normalized CBV and the 10th percentile histogram cutoff for ADC, adding intravoxel incoherent motion

to 90th percentile histogram cutoff for normalized CBV substantially improved the diagnostic accuracy for differentiating recurrent tumor and treatment from 86.8% to 92.3% for reader 1 and from 89.0% to 93.4% for reader 2, respectively. The intraclass correlation coefficients between readers were higher for perfusion parameters (intraclass correlation coefficient range, 0.84-0.89) than for diffusion parameters (intraclass correlation coefficient range, 0.68-0.79). **CONCLUSIONS:** Following gamma knife radiosurgery, intravoxel incoherent motion MR imaging can be used as a noninvasive imaging biomarker for differentiating recurrent tumor from treatment effect in patients with metastatic brain tumor.

[283] Impact of the number of metastatic brain lesions on survival after Gamma Knife radiosurgery.

Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2014;21(11):1928-33

Bashir A, Hodge CJ Jr, Dababneh H, Hussain M, Hahn S, Canute GW
PMID: 25037311 DOI: 10.1016/j.jocn.2014.03.026

Effectiveness of Gamma Knife radiosurgery (GKRS: Elekta AB, Stockholm, Sweden) for patients with metastatic brain disease and the prognostic factors influencing their survival were analyzed in a 5 year retrospective data analysis (July 2001 to June 2006). Kaplan-Meier survival curves were constructed using univariate and multivariate analyses with the respective salient prognostic factors. This study analyzed data on 330 patients with brain metastases who underwent GKRS. Lung carcinoma (55%) was the most common primary cancer followed by breast (17.8%), melanoma (9.4%), colorectal (4.8%) and renal (3.9%). The median survival for all patients was 8 months. Survival ranged from 13 months for breast metastases, 10 months for renal, and 8 months for lung to 5 months for colorectal and melanoma. Mean age of patients was 58.5 years (range 18-81). Melanoma patients were younger with a mean age of 49 and also had the highest number of lesions (3.8) when compared to patients with renal (2.5), lung (2.8), colorectal (3) and breast (3.6). When stratified according to the number of lesions patient survival was 8 months (one to three lesions), 7.5 months (four or five lesions) and 7 months (six lesions or more). Mean Karnofsky Performance Status score (KPS) was 77 and survival dropped significantly from 8 months to 4.5 months if KPS was less than 70. Survival improved with a KPS of 70 or more, regardless of the number of lesions treated. Selection of patients based on the number of lesions may not be justified. A prospective trial is required to further define the prognostic factors affecting survival.

[284] Stereotactic radiosurgery for brain metastases: a case-matched study comparing treatment results for patients 80 years of age or older versus patients 65-79 years of age.

Journal of neurosurgery. 2014;121(5):1148-57

Watanabe S, Yamamoto M, Sato Y, Kawabe T, Higuchi Y, Kasuya H, Yamamoto T, Matsumura A, Barford BE

PMID: 25061863 DOI: 10.3171/2014.6.JNS132790

OBJECT: Recently, an increasing number of patients with brain metastases, even patients over 80 years of age, have been treated with stereotactic radiosurgery (SRS). However, there is little information on SRS treatment results for patients with brain metastases 80 years of age and older. The authors undertook this study to reappraise whether SRS treatment results for patients 80 years of age or older differ from those of patients who are 65-79 years old. **METHODS:** This was an institutional review board-approved, retrospective cohort study. Among 2552 consecutive brain metastasis patients who underwent SRS during the 1998-2011 period, we studied 165 who were 80 years of age or older (Group A) and 1181 who were age 65-79 years old (Group B). Because of the remarkable disproportion in patient numbers between the 2 groups and considerable differences in pre-SRS clinical factors, the authors conducted a case-matched study using the propensity score matching method. Ultimately, 330 patients (165 from each group, A and B) were selected. For time-to-event outcomes, the Kaplan-Meier method was used to estimate overall survival and competing risk analysis was used to estimate other study end points, as appropriate. **RESULTS:** Although the case-matched study showed that post-SRS median survival

time (MST, months) was shorter in Group A patients (5.3 months, 95% CI 3.9-7.0 months) than in Group B patients (6.9 months, 95% CI 5.0-8.1 months), this difference was not statistically significant (HR 1.147, 95% CI 0.921-1.429, $p = 0.22$). Incidences of neurological death and deterioration were slightly lower in Group A than in Group B patients (6.3% vs 11.8% and 8.5% vs 13.9%), but these differences did not reach statistical significance ($p = 0.11$ and $p = 0.16$). Furthermore, competing risk analyses showed that the 2 groups did not differ significantly in cumulative incidence of local recurrence (HR 0.830, 95% CI 0.268-2.573, $p = 0.75$), rates of repeat SRS (HR 0.738, 95% CI 0.438-1.242, $p = 0.25$), or incidence of SRS-related complications (HR 0.616, 95% CI 0.152-2.495, $p = 0.49$). Among the Group A patients, post-SRS MSTs were 11.6 months (95% CI 7.8-19.6 months), 7.9 months (95% CI 5.2-10.9 months), and 2.8 months (95% CI; 2.4-4.6 months) in patients whose disease status was modified-recursive partitioning analysis (RPA) Class(es) I+IIa, IIb, and IIc+III, respectively ($p < 0.001$). **CONCLUSIONS:** Our results suggest that patients 80 years of age or older are not unfavorable candidates for SRS as compared with those 65-79 years old. Particularly, even among patients 80 years and older, those with modified-RPA Class I+IIa or IIb disease are considered to be favorable candidates for more aggressive treatment of brain metastases.

[285] Clinical benefit of 11C methionine PET imaging as a planning modality for radiosurgery of previously irradiated recurrent brain metastases.

Clinical nuclear medicine. 2014;39(11):939-43

Momose T, Nariai T, Kawabe T, Inaji M, Tanaka Y, Watanabe S, Maehara T, Oda K, Ishii K, Ishiwata K, Yamamoto M

PMID: 25140562 DOI: 10.1097/RLU.0000000000000561

OBJECT: Stereotactic radiosurgery with gamma knife (GK-SRS) generally improves the focal control of brain metastases. Yet in cases of focal recurrence at a previous radiation site, MRI is often imperfect in differentiating between active tumor and radiation injury. We have examined whether the use of C methionine (MET) with PET will facilitate this differentiation and improve the outcome of GK-SRS for focally recurrent brain metastases after prior treatment. **METHODS:** Eighty-eight patients underwent GK-SRS for postirradiation recurrent brain metastases. Thirty-four patients received radiation in areas manifesting high MET uptake (PET group) in a dose-planning procedure using MET-PET/MRI fusion images. Fifty-four patients referred from other institutes received radiation based on dose planning information obtained from MRI (MRI group). **RESULTS:** Sex, age, and the ratio of breast cancer differed significantly between the MRI and PET groups. The total irradiation volume was significantly smaller in the PET group, and the minimal irradiation dose was significantly higher. In a multivariable statistical analysis, the use of MET-PET ($P = 0.02$) was independently associated with prolonged overall survival after treatment, Karnofsky performance status ($P = 0.002$), the number of lesions ($P = 0.03$), and patient's sex ($P = 0.02$). The median survival time was significantly longer in the PET group (18.1 months) than in the MRI group (8.6 months) ($P = 0.01$). **CONCLUSION:** 11C methionine-PET/MRI fusion images for dose planning lengthened survival in patients undergoing GK-SRS for focally recurrent brain metastases.

[286] Relevance of gamma knife radiosurgery alone for the treatment of non-small cell lung cancer brain metastases.

Clinical neurology and neurosurgery. 2014;125:87-93

Zairi F, Ouammou Y, Le Rhun E, Aboukais R, Blond S, Vermandel M, Deken V, Devos P, Reyns N

PMID: 25108698 DOI: 10.1016/j.clineuro.2014.07.030

BACKGROUND AND PURPOSE: Stereotactic radiosurgery (SRS) followed by close follow-up is becoming a popular strategy for the management of brain metastases as cancer patients live longer and late adverse effects of whole brain radiotherapy (WBRT) are increasingly reported. The authors report their experience in consecutively treated patients with limited brain metastases from non-small cell lung cancer (NSCLC), who underwent SRS alone followed by a close follow-up. **METHODS:** This study is the retrospective analysis of prospectively collected data. We included of 89 consecutive patients (80 men;

mean age 59.7 years) with a KPS score of 60 or greater, who underwent Gamma Knife SRS for 1-4 metastases, at Lille University Hospital between January 2004 and December 2010. The mean radiation dose was 23.41Gy (range 18-26Gy) and the mean tumour volume was 2.47cm³ (range 0.3-6.7cm³). After treatment, clinical and radiological (MRI) monitoring was scheduled at 2, 4, 8 and 12 months in the first year and at 4-month intervals thereafter. **RESULTS:** Overall survival was 70.8% at 1 year and 50% at 2 years. The actuarial local control rate was 91.5% at 1 year and 85.5% at 2 years. Ten of 89 patients experienced a local failure, which required a salvage treatment. The distant brain control rate was 79.2% at 1 year, and 67.1% at 2 years. A total of 25 patients developed new metastases, 10 patients were treated with a new radiosurgical procedure, 12 patients underwent a WBRT while 3 patients developed a leptomeningeal disease. We reported an overall complication rate of 10.1% per patient and 7.8% per treated tumour; all complications were classified grade 1 or 2. **CONCLUSION:** In patients with limited brain metastases from NSCLC, SRS is an effective treatment associated with high local control rate with low morbidity. When performed in isolation, close follow-up is mandatory and radiosurgery can be renewed as salvage treatment for distant brain progression, limiting the use of WBRT.

[287] On demand Gamma-Knife strategy can be safely combined with BRAF inhibitors for the treatment of melanoma brain metastases.

Annals of oncology : official journal of the European Society for Medical Oncology. 2014;25(10):2086-2091

Gaudy-Marqueste C, Carron R, Delsanti C, Loundou A, Monestier S, Archier E, Richard MA, Regis J, Grob JJ

PMID: 25057167 DOI: 10.1093/annonc/mdu266

BACKGROUND: Both Gamma-Knife radiosurgery (GKRS) and BRAF inhibitors (BRAF-I) have been shown to be useful in melanoma patients with brain metastases (BMs), thus suggesting that it could be interesting to combine their respective advantages. However, cases of radiosensitization following conventional radiation therapy in BRAF-I treated patients have raised serious concerns about the real feasibility and risk/benefit ratio of this combination.

PATIENTS AND METHODS: Review by two independent observers of brain magnetic resonance imaging (MRI) follow-up pictures, and volume and edema quantifications, and survival assessment in all patients who had been treated by GKRS and BRAF-I at a single institution. **RESULTS:** Among 53 GKRS carried out in 30 patients who ever received BRAF-I and GKRS, 33 GKRS were carried out in 24 patients while under BRAF-I treatment, from which only 4 with an interruption of BRAF-I. The 20 other GKRS were carried out in 15 patients (including 9 of the 24) before initiation of BRAF-I treatment. No case of radiation-induced necrosis and no scalp radiation dermatitis occurred. A >20% increase in volume was observed in 35 of the 263 BM treated by GKRS (13.3%), but only 3 clear-cut edemas and 3 hemorrhages were detected within 2 months after GKRS, and 4 edemas and 7 hemorrhages later. Neither the MRI features nor the incidence of the volume changes, hemorrhage and edema were deemed unexpected for melanoma BM treated by GKRS. Median survival from first GKRS under BRAF-I and first dose of BRAF-I were 24.8 and 48.8 weeks, respectively. **CONCLUSION:** This series does not show immediate radiotoxicity nor radiation recall, in melanoma patients with BRAF-I whose BMs are treated by GKRS. Interrupting BRAF-I for stereotactic radiosurgery (SRS) of BM seems useless, although it is still advised for other radiation therapies. The potential benefit of combining SRS and BRAF-I can be safely tested.

[288] Survival after surgery and stereotactic radiosurgery for patients with multiple intracranial metastases: results of a single-center retrospective study.

Journal of neurosurgery. 2014;121(4):839-45

Smith TR, Lall RR, Lall RR, Abecassis IJ, Arnaout OM, Marymont MH, Swanson KR, Chandler JP

PMID: 24857242 DOI: 10.3171/2014.4.JNS13789

OBJECTIVES: Patients with systemic cancer and a single brain metastasis who undergo treatment with resection plus radiotherapy live longer and have a

better quality of life than those treated with radiotherapy alone. Historically, whole-brain radiotherapy (WBRT) has been the mainstay of radiation therapy; however, it is associated with significant delayed neurocognitive sequelae. In this study, the authors looked at survival in patients with single and multiple intracranial metastases who had undergone surgery and adjuvant stereotactic radiosurgery (SRS) to the tumor bed and synchronous lesions. **METHODS:** The authors retrospectively reviewed the records from an 8-year period at a single institution for consecutive patients with brain metastases treated via complete resection of dominant lesions and adjuvant radiosurgery. The cohort was analyzed for time to local progression, synchronous lesion progression, new intracranial lesion development, systemic progression, and overall survival. The Kaplan-Meier method (stratified by age, sex, tumor histology, and number of intracranial lesions prior to surgery) was used to calculate both progression-free and overall survival. A Cox proportional-hazards regression model was also fitted with the number of intracranial lesions as the predictor and survival as the outcome controlling for disease severity, age, sex, and primary histology. **RESULTS:** The median overall follow-up among the 150-person cohort eligible for analysis was 17 months. Patients had an average age of 46.2 years (range 16-82 years), and 62.7% were female. The mean (+/- standard deviation) number of intracranial lesions per patient was 2.5 +/- 2.3. The mean time between surgery and stereotactic radiosurgery (SRS) was 3.2 +/- 4.1 weeks. Primary cancers included lung cancer (43.3%), breast cancer (21.3%), melanoma (10.0%), renal cell carcinoma (6.7%), and colon cancer (6.7%). The average number of isocenters per treated lesion was 7.6 +/- 6.6, and the average treatment dose was 17.8 +/- 2.8 Gy. One-year survival for patients in this cohort was 52%, and the 1-year local control rate was 77%. The median (+/- standard error) overall survival was 13.2 +/- 1.9 months. There was no difference in survival between patients with a single lesion and those with multiple lesions (p = 0.319) after controlling for age, sex, and histology of primary tumor. Patients with primary breast histology had the greatest overall median survival (22.9 +/- 6.2 months); patients with colorectal cancer had the shortest overall median survival (5.3 +/- 1.8 months). The most common cause of death in this series was systemic progression (79%). **CONCLUSIONS:** These results confirm that 1-year survival for patients with multiple intracranial metastases treated with resection followed by SRS to both the tumor bed and synchronous lesions is similar to established outcomes for patients with a single intracranial metastasis.

[289] Risk factors for leptomeningeal carcinomatosis in patients with brain metastases who have previously undergone stereotactic radiosurgery.

Journal of neuro-oncology. 2014;120(1):163-9

Huang AJ, Huang KE, Page BR, Ayala-Peacock DN, Lucas JT Jr, Lesser GJ, Laxton AW, Tatter SB, Chan MD

PMID: 25048529 DOI: 10.1007/s11060-014-1539-6

Our objective was to explore the hypothesis that the risk of leptomeningeal dissemination (LMD) in patients who underwent stereotactic radiosurgery (SRS) for brain metastases is influenced by the site of the primary cancer, the addition of whole brain radiation therapy (WBRT), surgical resection, and control over their systemic disease. We conducted a retrospective cohort analysis of 805 patients who were treated with SRS for brain metastases between 1999 and 2012 at the Wake Forest Baptist Medical Center, and excluded all patients with evidence of LMD before SRS. The primary outcome was LMD. Forty-nine of 795 patients developed LMD with a cumulative incidence of 6.2% (95% Confidence Interval (CI), 4.7-8.0). Median time from SRS to LMD was 7.4 months (Interquartile Range (IQR), 3.3-15.4). A colorectal primary site (Hazard Ratio (HR), 4.5; 95% CI 2.5-8.0; p < 0.0001), distant brain failure (HR, 2.0; 95% CI 1.2-3.2; p = 0.007), breast primary site (HR, 1.6; 95% CI 1.0-2.7; p = 0.05), the number of intracranial metastases at time of initial SRS (HR, 1.1; 95% CI 1.0-1.2; p = 0.02), and age (by 5-year interval) (HR, 0.9; 95% CI 0.8, 0.9; p = 0.0006) were independent factors associated with LMD. There was no evidence that surgical resection before SRS altered the risk of LMD (HR, 1.1; 95% CI 0.6-2.0, p = 0.78). In patients who underwent SRS for brain metastases, a colorectal or breast primary site, distant brain failure, younger age, and an increased number of intracranial metastases were independently

associated with LMD. Given its relative rarity as an outcome, multi-institutional prospective studies will likely be necessary to validate and quantify these relationships.

[290] Predictors of individual tumor local control after stereotactic radiosurgery for non-small cell lung cancer brain metastases.

International journal of radiation oncology, biology, physics. 2014;90(2):407-13
Garsa AA, Badiyan SN, DeWees T, Simpson JR, Huang J, Drzymala RE, Barani JJ, Dowling JL, Rich KM, Chicoine MR, Kim AH, Leuthardt EC, Robinson CG
PMID: 25084610 DOI: 10.1016/j.ijrobp.2014.05.047

PURPOSE: To evaluate local control rates and predictors of individual tumor local control for brain metastases from non-small cell lung cancer (NSCLC) treated with stereotactic radiosurgery (SRS). **METHODS AND MATERIALS:** Between June 1998 and May 2011, 401 brain metastases in 228 patients were treated with Gamma Knife single-fraction SRS. Local failure was defined as an increase in lesion size after SRS. Local control was estimated using the Kaplan-Meier method. The Cox proportional hazards model was used for univariate and multivariate analysis. Receiver operating characteristic analysis was used to identify an optimal cutpoint for conformality index relative to local control. A P value $<.05$ was considered statistically significant. **RESULTS:** Median age was 60 years (range, 27-84 years). There were 66 cerebellar metastases (16%) and 335 supratentorial metastases (84%). The median prescription dose was 20 Gy (range, 14-24 Gy). Median overall survival from time of SRS was 12.1 months. The estimated local control at 12 months was 74%. On multivariate analysis, cerebellar location (hazard ratio [HR] 1.94, $P=.009$), larger tumor volume (HR 1.09, $P<.001$), and lower conformality (HR 0.700, $P=.044$) were significant independent predictors of local failure. Conformality index cutpoints of 1.4-1.9 were predictive of local control, whereas a cutpoint of 1.75 was the most predictive ($P=.001$). The adjusted Kaplan-Meier 1-year local control for conformality index ≥ 1.75 was 84% versus 69% for conformality index <1.75 , controlling for tumor volume and location. The 1-year adjusted local control for cerebellar lesions was 60%, compared with 77% for supratentorial lesions, controlling for tumor volume and conformality index. **CONCLUSIONS:** Cerebellar tumor location, lower conformality index, and larger tumor volume were significant independent predictors of local failure after SRS for brain metastases from NSCLC. These results warrant further investigation in a prospective setting.

[291] A nomogram for predicting distant brain failure in patients treated with gamma knife stereotactic radiosurgery without whole brain radiotherapy.

Neuro-oncology. 2014;16(9):1283-8
Ayala-Peacock DN, Peiffer AM, Lucas JT, Isom S, Kuremsky JG, Urbanic JJ, Bourland JD, Laxton AW, Tatter SB, Shaw EG, Chan MD
PMID: 24558022 DOI: 10.1093/neuonc/nou018

BACKGROUND: We review our single institution experience to determine predictive factors for early and delayed distant brain failure (DBF) after radiosurgery without whole brain radiotherapy (WBRT) for brain metastases. **MATERIALS AND METHODS:** Between January 2000 and December 2010, a total of 464 patients were treated with Gamma Knife stereotactic radiosurgery (SRS) without WBRT for primary management of newly diagnosed brain metastases. Histology, systemic disease, RPA class, and number of metastases were evaluated as possible predictors of DBF rate. DBF rates were determined by serial MRI. Kaplan-Meier method was used to estimate rate of DBF. Multivariate analysis was performed using Cox Proportional Hazard regression. **RESULTS:** Median number of lesions treated was 1 (range 1-13). Median time to DBF was 4.9 months. Twenty-seven percent of patients ultimately required WBRT with median time to WBRT of 5.6 months. Progressive systemic disease ($\chi^2=16.748$, $P<.001$), number of metastases at SRS ($\chi^2=27.216$, $P<.001$), discovery of new metastases at time of SRS ($\chi^2=9.197$, $P<.01$), and histology ($\chi^2=12.819$, $P<.07$) were factors that predicted for earlier time to distant failure. High risk histologic subtypes (melanoma, her2 negative breast, $\chi^2=11.020$, $P<.001$) and low risk subtypes (her2 + breast, $\chi^2=11.343$, $P<.001$) were identified.

Progressive systemic disease ($\chi^2=9.549$, $P<.01$), number of brain metastases ($\chi^2=16.953$, $P<.001$), minimum SRS dose ($\chi^2=21.609$, $P<.001$), and widespread metastatic disease ($\chi^2=29.396$, $P<.001$) were predictive of shorter time to WBRT. **CONCLUSION:** Systemic disease, number of metastases, and histology are factors that predict distant failure rate after primary radiosurgical management of brain metastases.

[292] Volumetric response to radiosurgery for brain metastasis varies by cell of origin.

Journal of neurosurgery. 2014;121(3):564-9
Iyer A, Harrison G, Kano H, Weiner GM, Luther N, Niranjana A, Flickinger JC, Lunsford LD, Kondziolka D
PMID: 24878286 DOI: 10.3171/2014.4.JNS131502
OBJECT: The aim of this study was to evaluate the imaging response of brain metastases after radiosurgery and to correlate the response with tumor type and patient survival. **METHODS:** The authors conducted a retrospective review of patients who had undergone Gamma Knife radiosurgery for brain metastases from non-small cell lung cancer (NSCLC), breast cancer, or melanoma. The imaging volumetric response by tumor type was plotted at 3-month intervals and classified as a sustained decrease in tumor volume (Type A), a transient decrease followed by a delayed increase in tumor volume (Type B), or a sustained increase in tumor volume (Type C). These imaging responses were then compared with patient survival and tumor type. **RESULTS:** Two hundred thirty-three patients with metastases from NSCLC (96 patients), breast cancer (98 patients), and melanoma (39 patients) were eligible for inclusion in this study. The patients with NSCLC were most likely to exhibit a Type A response; those with breast cancer, a Type B response; and those with melanoma, a Type C response. Among patients with NSCLC, the median overall survival was 11.2 months for those with a Type A response (76 patients), 8.6 months for those with a Type B response (6 patients), and 10.5 months for those with a Type C response (14 patients). Among patients with breast cancer, the median overall survival was 16.6 months in those with a Type A response (65 patients), 18.1 months in those with a Type B response (20 patients), and 7.5 months in those with a Type C response (13 patients). For patients with melanoma, the median overall survival was 5.2 months in those with a Type A response (26 patients) and 6.7 months in those with a Type C response (13 patients). None of the patients with melanoma had a Type B response. The imaging response was significantly associated with survival only in patients with breast cancer. **CONCLUSIONS:** The various types of imaging responses of metastatic brain tumors after stereotactic radiosurgery depend in part on tumor type. However, the type of response only correlates with survival in patients with breast cancer.

[293] Upfront stereotactic radiosurgery in patients with brain metastases from small cell lung cancer: retrospective analysis of 41 patients.

Radiation oncology (London, England). 2014;9:152
Yomo S, Hayashi M
PMID: 25005424 DOI: 10.1186/1748-717X-9-152
BACKGROUND: Although the efficacy of prophylactic or therapeutic whole brain radiotherapy (WBRT) for brain metastases (BM) from small cell lung cancer (SCLC) is well established, the role of stereotactic radiosurgery (SRS) has yet to be determined. In the present retrospective analysis, we investigated whether upfront SRS might be an effective treatment option for patients with BM from SCLC. **METHODS:** We analyzed 41 consecutive patients with a limited number of BM (≤ 10) from SCLC who received SRS as the initial treatment. No prophylactic and therapeutic WBRT was given prior to SRS. The median patient age was 69 years and the median Karnofsky performance status (KPS) score was 90. Repeat SRS was given for new distant lesions detected on follow-up neuroradiological imaging, as necessary. Overall survival, neurological death, and local and distant BM recurrence rates were analyzed. The survival results were tested with three prognostic scoring systems validated for SCLC: Diagnosis-specific graded prognostic assessment (DS-GPA), Radiation therapy oncology group -recursive

partitioning analysis and Rades's survival score. **RESULTS:** One- and 2-year overall survival rates were 44% and 17%, respectively. The median survival time was 8.1 months. Survival results replicated the DS-GPA ($P = 0.022$) and Rades's survival score ($P = 0.034$). On multivariate analysis, patients with high KPS (hazard ratio (HR): 0.308, $P = 0.009$) and post-SRS chemotherapy (HR: 0.324, $P = 0.016$) had better overall survival. In total, 95/121 tumors (79%) in 34 patients (83%) with sufficient radiological follow-up data were evaluated. Six- and 12-month rates of local control failure were 0% and 14%, respectively. Six- and 12-month distant BM rates were 22% and 44%, respectively. Repeat SRS, salvage WBRT and microsurgery were subsequently required in 18, 7 and one patient, respectively. Symptomatic radiation injury developed in two patients and both were treated conservatively. **CONCLUSIONS:** Our survival analyses with the validated prognostic grading systems suggested upfront SRS for limited BM from SCLC to be a potential treatment option, with patient survival being slightly more than eight months after SRS. Although SRS provided durable local tumor control, repeat treatment was needed in nearly half of patients to achieve control of distant BM.

[294] Decision analysis of stereotactic radiation surgery versus stereotactic radiation surgery and whole-brain radiation therapy for 1 to 3 brain metastases. *International journal of radiation oncology, biology, physics.* 2014;89(3):563-8
Lester-Coll NH, Dosoretz AP, Yu JB
PMID: 24751412 DOI: 10.1016/j.ijrobp.2014.03.001

PURPOSE: Although whole-brain radiation therapy (WBRT) is effective for controlling intracranial disease, it is also associated with neurocognitive side effects. It is unclear whether a theoretically improved quality of life after stereotactic radiation surgery (SRS) alone relative to that after SRS with adjuvant WBRT would justify the omission of WBRT, given the higher risk of intracranial failure. This study compares SRS alone with SRS and WBRT, to evaluate the theoretical benefits of intracranial tumor control with adjuvant WBRT against its possible side effects, using quality-adjusted life expectancy (QALE) as a primary endpoint. **METHODS AND MATERIALS:** A Markov decision analysis model was used to compare QALE in a cohort of patients with 1 to 3 brain metastases and Karnofsky performance status of at least 70. Patients were treated with SRS alone or with SRS immediately followed by WBRT. Patients treated with SRS alone underwent surveillance magnetic resonance imaging and received salvage WBRT if they developed intracranial relapse. All patients whose cancer relapsed after WBRT underwent simulation as dying of intracranial progression. Model parameters were estimated from published literature. **RESULTS:** Treatment with SRS yielded 6.2 quality-adjusted life months (QALMs). The addition of initial WBRT reduced QALE by 1.2 QALMs. On one-way sensitivity analysis, the model was sensitive only to a single parameter, the utility associated with the state of no evidence of disease after SRS alone. At values greater than 0.51, SRS alone was preferred. **CONCLUSIONS:** In general, SRS alone is suggested to have improved quality of life in patients with 1 to 3 brain metastases compared to SRS and immediate WBRT. Our results suggest that immediate treatment with WBRT after SRS can be reserved for patients who would have a poor performance status regardless of treatment. These findings are stable under a wide range of assumptions.

[295] Long-term outcome of gamma knife radiosurgery for metastatic brain tumors originating from lung cancer. *Surgical neurology international.* 2014;5(Suppl 8):S396-403
Bir SC, Ambekar S, Bollam P, Nanda A
PMID: 25289169 DOI: 10.4103/2152-7806.140197

BACKGROUND: Gamma knife radiosurgery (GKRS) has emerged as an important treatment option for metastatic brain tumors (MBTs). However, the long-term outcome of GKRS on MBTs originating from lung carcinoma is not well understood. The treatment of MBTs derived from lung cancer with GKRS at our institution is reviewed. **METHODS:** We performed a retrospective review (2000-2013) of 173 patients with MBTs from lung cancer who received GKRS. Out of

173 patients, 38 patients had recurrent tumors after microsurgical resection and whole brain radiotherapy (WBRT). **RESULTS:** GKRS in MBTs metastasized from lung carcinoma showed significant variations in tumor growth control (decreased in 79 [45.7%] patients, arrested growth in 54 [31.2%] patients, and increased tumor size in 40 [23.1%] patients). The median survival in the study population was 14 months. Overall survival after 3 years was 25%, whereas progression-free survival after 3 years was 45%. The predictive factors for improving survival in the patients with MBTs were recursive partitioning analysis (RPA) class I ($P = 0.005$), absence of hydrocephalus ($P = 0.001$), Karnofsky performance scale (KPS) >70 ($P = 0.007$), age ≤ 65 ($P = 0.041$), tumor size ≤ 3 cm ($P = 0.023$), controlled primary tumor ($P = 0.049$), and single number of MBTs ($P = 0.044$). **CONCLUSION:** Long-term follow-up revealed that GKRS offers a high rate of tumor control and good overall survival period in both new and recurrent patients with MBTs originating from lung carcinoma. Thus, GKRS is an effective treatment option for new patients with MBTs from lung cancer, as well as an adjuvant therapy in patients with recurrent MBTs derived from lung cancer.

[296] A minimally invasive treatment option for large metastatic brain tumors: long-term results of two-session Gamma Knife stereotactic radiosurgery. *Radiation oncology (London, England).* 2014;9:132

Yomo S, Hayashi M

PMID: 24917309 DOI: 10.1186/1748-717X-9-132

BACKGROUND: Large brain metastases (BM) remain a significant cause of morbidity and death for cancer patients despite current advances in multimodality therapies. The goal of the present study was to evaluate the efficacy and limitations of 2-session Gamma Knife stereotactic radiosurgery (SRS) for patients with large BM. **METHODS:** This is a prospective, open-label and single arm study analyzing 58 consecutive patients who received 2-session SRS for large BM (≥ 10 mL). The median age was 66 years, and the median Karnofsky performance status (KPS) score was 70. SRS was the initial treatment in 51 large tumors (84%) and was used as salvage after failed prior treatments for 10 tumors (16%). The fraction protocol was 20-30 Gy given in 2 fractions with 3-4 weeks between fractions. Overall survival (OS) and neurological death (ND), local tumor control and KPS were analyzed. **RESULTS:** The median follow-up time was 9.0 months. One- and 2-year OS rates were 47% and 20%, respectively. The median OS time was 11.8 months (95% CI: 5.5-15.6). The causes of death were intracranial local progression in 5 cases, meningeal carcinomatosis in 3 and progression of the primary lesion in 39. One- and 2-year ND-free survival rates were 91% and 84%, respectively. In 52 of 61 large BM (85%) with sufficient radiological follow-up data, 6- and 12-month local tumor control rates were 85% and 64%, respectively. The mean KPS improved from 70 at the 1st SRS to 82 at the 2nd; the first follow-up mean KPS was 87 ($P < 0.001$). Symptomatic radiation injury developed and required conservative treatment in 3 patients (5%). **CONCLUSIONS:** Long-term follow-up showed that two-session Gamma Knife SRS achieved durable tumor control rates as well as acceptable treatment-related morbidity. This treatment method may potentially merit being offered to patients with large BM who are in poor condition or are otherwise ineligible for standard care.

[297] Gamma Knife radiosurgery to four or more brain metastases in patients without prior intracranial radiation or surgery.

Cancer medicine. 2014;3(3):565-71

Ojerholm E, Lee JY, Kolker J, Lustig R, Dorsey JF, Alonso-Basanta M

PMID: 24510602 DOI: 10.1002/cam4.206

Data on stereotactic radiosurgery (SRS) for four or more metastases are limited. Existing studies are confounded by significant proportions of patients receiving prior whole-brain radiation therapy (WBRT) or concurrent WBRT with SRS. Furthermore, published results disagree about the impact of tumor volume on overall survival. A retrospective review identified 38 patients without prior intracranial radiation or surgery who received Gamma Knife (GK) as sole treatment to ≥ 4 brain metastases in a single session. Twenty-eight cases with follow-up imaging were analyzed for intracranial progression. Prognostic factors were

examined by univariate (log-rank test) and multivariate (Cox proportional hazards model) analyses. Common primary tumors were non-small cell lung (45%), melanoma (37%), and breast (8%). Cases were recursive partitioning analysis class II (94%) or III (6%). Patients harbored a median five tumors (range 4-12) with median total tumor volume of 1.2 cc. A median dose of 21 Gy was prescribed to the 50% isodose line. Patients survived a median 6.7 months from GK. Local treatment failure occurred in one case (4%) and distant failure in 22 (79%). On multivariate analysis, total tumor volume ≥ 3 cc was significantly associated with distant failure and worsened overall survival ($P = 0.042$ and 0.040). Fourteen patients (37%) underwent salvage WBRT at a median 10.3 months from GK and seven patients received repeat GK. GK as sole initial treatment for four or more simultaneous metastases spares some patients WBRT and delays it for others. Increased total tumor volume (≥ 3 cc) is significantly associated with worsened overall survival.

[298] Application of diffusion-weighted magnetic resonance imaging to predict the intracranial metastatic tumor response to gamma knife radiosurgery.

Journal of neuro-oncology. 2014;118(2):351-361

Lee CC, Wintermark M, Xu Z, Yen CP, Schlesinger D, Sheehan JP

PMID: 24760414 DOI: 10.1007/s11060-014-1439-9

To evaluate the effect of stereotactic radiosurgery (SRS) on intracranial metastases with diffusion-weighted imaging/apparent diffusion coefficient maps. A total of 107 patients with 144 metastases larger than 1 cm in diameter were retrospectively reviewed. We calculated the DWI(Tumor/white matter) ratios (DWI(T/WM) ratio) between the metastases and the normal, contralateral frontal white matter at each time point. We also recorded the ADC values for metastases (ADCT values). The DWI(T/WM) ratio and ADCT values were assessed for correlation with the patients' tumor response, brain edema, and survival. A decrease in DWI(T/WM) ratios was seen in the controlled metastases, and an increase in the DWI(T/WM) ratio were seen in the metastases with poor tumor control. On the other hand, an increase in ADCT values was seen in the controlled metastases, and a decrease in ADCT values was seen in the metastases with poor control. The differences were significant (p value: 0.001 and 0.002, respectively). Sensitivity of a decrease in the DWI(T/WM) ratio to make an early prediction of tumor control was 83.9%, and specificity was 88.5%. When using the initial ADCT values of metastases to predict tumor response, sensitivity and specificity were 85.5 and 72.7%, respectively. DWI/ADC is a practical method for studying the efficacy of SRS and predicting early metastases response progression. A decrease signal on DWI and increased ADC values are indicators of good tumor control, and reflect the beneficial effect of SRS.

[299] Gamma knife treatment of brainstem metastases.

International journal of molecular sciences. 2014;15(6):9748-61

Peterson HE, Larson EW, Fairbanks RK, MacKay AR, Lamoreaux WT, Call JA,

Carlson JD, Ling BC, Demakas JJ, Cooke BS, Peressini B, Lee CM

PMID: 24886816 DOI: 10.3390/ijms15069748

The management of brainstem metastases is challenging. Surgical treatment is usually not an option, and chemotherapy is of limited utility. Stereotactic radiosurgery has emerged as a promising palliative treatment modality in these cases. The goal of this study is to assess our single institution experience treating brainstem metastases with Gamma Knife radiosurgery (GKRS). This retrospective chart review studied 41 patients with brainstem metastases treated with GKRS. The most common primary tumors were lung, breast, renal cell carcinoma, and melanoma. Median age at initial treatment was 59 years. Nineteen (46%) of the patients received whole brain radiation therapy (WBRT) prior to or concurrent with GKRS treatment. Thirty (73%) of the patients had a single brainstem metastasis. The average GKRS dose was 17 Gy. Post-GKRS overall survival at six months was 42%, at 12 months was 22%, and at 24 months was 13%. Local tumor control was achieved in 91% of patients, and there was one patient who had a fatal brain hemorrhage after treatment. Karnofsky performance score (KPS) >80 and the absence of prior WBRT were predictors for improved survival on multivariate

analysis (HR 0.60 ($p = 0.02$), and HR 0.28 ($p = 0.02$), respectively). GKRS was an effective treatment for brainstem metastases, with excellent local tumor control.

[300] Change in postsurgical cavity size within the first 30 days correlates with extent of surrounding edema: consequences for postoperative radiosurgery.

Journal of computer assisted tomography. 2014;38(3):457-60

Ahmed S, Hamilton J, Colen R, Schellingerhout D, Vu T, Rao G, McAleer MF, Mahajan A

PMID: 24681852 DOI: 10.1097/RCT.0000000000000058

OBJECTIVE: Resection cavity diameter of less than 40 mm is required to be eligible for stereotactic radiosurgery (SRS), after gross total resection of brain metastasis at our institution. Our study evaluates the correlation between vasogenic edema and change in cavity size for 30 days. **METHODS:** Cavity size was measured on the postoperative and follow-up magnetic resonance imaging. Vasogenic edema was quantified as the largest axial measurement of T2 hyperintensity surrounding the resection cavity (postoperative magnetic resonance imaging). **RESULTS:** Thirty-nine resection cavities (37 patients) were reviewed. There was a statistically significant (Pearson coefficient = -0.35; $P = 0.02$) negative correlation between edema and change in cavity size. An arbitrary cutoff value of a 15-mm edema yielded a sensitivity of 96% and a specificity of 65% ($P < 0.001$) to predict 10% decrease in cavity size. **CONCLUSIONS:** In patients with cavity size close to the size cutoff for SRS, rescanning closer to the date of SRS should be considered, especially if there is significant edema surrounding the cavity.

[301] Gamma knife radiosurgery for management of cerebral metastases from esophageal carcinoma.

Journal of neuro-oncology. 2014;118(1):141-6

Bowden G, Kano H, Tempel ZJ, Caparosa E, Monaco E 3rd, Niranjana A, Flickinger J, Luketich JD, Lunsford LD

PMID: 24736828 DOI: 10.1007/s11060-014-1408-3

Esophageal carcinoma rarely results in intracranial metastases but when it does, the patient prognosis is grim. Because of its rarity outcomes after stereotactic radiosurgery (SRS) are not known. We sought to evaluate the outcomes of SRS in the management of esophageal cancer that has spread to the brain. This single institution retrospective analysis reviewed our experience with esophageal metastasis from 1987 to 2013. Thirty patients (36 SRS procedures) with a median age of 59 (37-86 years) underwent Gamma knife(R) SRS. The esophageal origin was adenocarcinoma in 26 patients (87%), squamous cell carcinoma in 3 patients (10%), and mixed neuroendocrine carcinoma in 1 patient (3%). Fifteen patients were treated for a single metastasis and 15 patients were treated for multiple metastases for a total of 87 tumors. The median tumor volume was 5.7 cm(3) (0.5-44 cm(3)) with a median marginal dose of 17 Gy (12-20 Gy). The median survival time from the diagnosis of brain metastasis was 8 months and the median survival from SRS was 4.2 months. This corresponded to a 6-month survival of 45% and a 12-month survival of 19% after SRS. A higher KPS at the time of procedure was associated with an increase in survival ($p = 0.023$). The local tumor control rate in this group was 92%. Four patients had repeat SRS for new metastatic deposits. One patient developed a new neurological deficit after SRS. SRS proved an effective means of providing local control for esophageal metastases to the brain. Concomitant systemic disease progression at the time of brain metastasis resulted in poor long-term survival.

[302] Clinical outcome of stereotactic radiosurgery for central nervous system metastases from renal cell carcinoma.

Clinical genitourinary cancer. 2014;12(2):111-6

Seastone DJ, Elson P, Garcia JA, Chao ST, Suh JH, Angelov L, Rini BI

PMID: 24331575 DOI: 10.1016/j.clgc.2013.10.001

BACKGROUND: Current treatment modalities for central nervous system (CNS) metastases from renal cell cancer (RCC) include surgical resection, stereotactic radiosurgery (SRS), and whole-brain radiotherapy. Existing studies describing

treatment outcomes for CNS metastases include multiple tumor types and thus provide little insight into how RCC CNS metastases respond to these modalities.

MATERIALS AND METHODS: RCC patients with brain metastases treated with SRS at the Cleveland Clinic between 1996 and 2010 were retrospectively identified. Radiosurgery and systemic therapy characteristics were recorded. Patients were followed up radiographically at 1 to 2 months after radiosurgery and every 3 to 6 months thereafter with magnetic resonance imaging scans. **RESULTS:** Of the 166 patients identified, local control was obtained in 90% of patients. In 38% of patients there were additional distant CNS metastases at a median of 12.8 months (95% CI, 8.5-21.1) after SRS. The median time to progression (either local or distant) was estimated to be 9.9 months (95% CI, 5.9-12.9). Higher (> 2.5) RCC-specific graded prognostic assessment (GPA) score was the only factor examined that was found to be a significant prognostic factor for improved outcome ($P = .02$); however, there was some suggestion that a single target lesion ($P = .07$) and age ≥ 60 years ($P = .07$) may also be associated with better CNS control. **CONCLUSION:** Stereotactic radiosurgery for a limited number of CNS metastases from RCC is associated with excellent local control and is an effective if not preferred treatment modality.

[303] Using higher isodose lines for gamma knife treatment of 1 to 3 brain metastases is safe and effective.

Neurosurgery. 2014;74(4):360-4; discussion 364-5; quiz 365-6
Shiue K, Barnett GH, Suh JH, Vogelbaum MA, Reddy CA, Weil RJ, Angelov L, Neyman G, Chao ST
PMID: 24448185 DOI: 10.1227/NEU.0000000000000289

BACKGROUND: Higher isodose lines (IDLs) in Gamma Knife (GK) Perfexion treatment of brain metastases (BMet) could result in lower local control (LC) or higher radiation necrosis (RN) rates, but reduce treatment time. **OBJECTIVE:** To assess the impact of the heterogeneity index (HI) and conformality index (CFI) on local failure (LF) for patients treated with GK for 1 to 3 BMet. **METHODS:** From an institutional review board-approved database, 320 patients with 496 BMet were identified, treated for 1 to 3 BMet from July 2007 to April 2011 on GK Perfexion. Cox proportional hazards regression was used to analyze significance of HI, CFI, IDL, dose, tumor diameter, recursive partitioning analysis class, tumor radioresistance, primary, smoking history, metastasis location, and whole-brain radiation therapy (WBRT) history with LF and RN. **RESULTS:** Median follow-up by lesion was 6.8 months (range, 0-49.6). The series median survival was 14.2 months. Per RECIST, 9.5% of lesions failed, 33.9% were stable, 38.3% partially responded, 17.1% responded completely, and 1.2% could not be assessed. The 12-month LC rate was 87.3%. On univariate analysis, a dose less than 20 Gy (hazard ratio [HR]: 2.940, $P < .001$); tumor size (HR: 1.674, $P < .001$); and cerebellum/brainstem location vs other (HR: 1.891, $P = .043$) were significant for LF. Non-small cell lung cancer (HR: 0.333, $P = .0097$) was associated with better LC. On multivariate analysis, tumor size (HR: 1.696, $P < .001$) and cerebellum/brainstem location vs other (HR: 1.959, $P = .033$) remained significant for LF. Variables not significant for LF included CI, IDL, and HI. **CONCLUSION:** Our study of patients with 1 to 3 BMet treated with GK demonstrated no difference in LC or RN with varying HI, indicating that physicians can treat to IDL at 70% or higher IDL to reduce treatment time without increased LF or RN.

[304] Stereotactic radiosurgery for patients with multiple brain metastases (JLKG0901): a multi-institutional prospective observational study.

The Lancet. Oncology. 2014;15(4):387-95
Yamamoto M, Serizawa T, Shuto T, Akabane A, Higuchi Y, Kawagishi J, Yamanaka K, Sato Y, Jokura H, Yomo S, Nagano O, Kenai H, Moriki A, Suzuki S, Kida Y, Iwai Y, Hayashi M, Onishi H, Gondo M, Sato M, Akimitsu T, Kubo K, Kikuchi Y, Shibasaki T, Goto T, Takanashi M, Mori Y, Takakura K, Saeki N, Kunieda E, Aoyama H, Momoshima S, Tsuchiya K
PMID: 24621620 DOI: 10.1016/S1470-2045(14)70061-0

BACKGROUND: We aimed to examine whether stereotactic radiosurgery without whole-brain radiotherapy (WBRT) as the initial treatment for patients with five

to ten brain metastases is non-inferior to that for patients with two to four brain metastases in terms of overall survival. **METHODS:** This prospective observational study enrolled patients with one to ten newly diagnosed brain metastases (largest tumour <10 mL in volume and <3 cm in longest diameter; total cumulative volume ≤ 15 mL) and a Karnofsky performance status score of 70 or higher from 23 facilities in Japan. Standard stereotactic radiosurgery procedures were used in all patients; tumour volumes smaller than 4 mL were irradiated with 22 Gy at the lesion periphery and those that were 4-10 mL with 20 Gy. The primary endpoint was overall survival, for which the non-inferiority margin for the comparison of outcomes in patients with two to four brain metastases with those of patients with five to ten brain metastases was set as the value of the upper 95% CI for a hazard ratio (HR) of 1.30, and all data were analysed by intention to treat. The study was finalised on Dec 31, 2012, for analysis of the primary endpoint; however, monitoring of stereotactic radiosurgery-induced complications and neurocognitive function assessment will continue for the censored subset until the end of 2014. This study is registered with the University Medical Information Network Clinical Trial Registry, number 000001812. **FINDINGS:** We enrolled 1194 eligible patients between March 1, 2009, and Feb 15, 2012. Median overall survival after stereotactic radiosurgery was 13.9 months [95% CI 12.0-15.6] in the 455 patients with one tumour, 10.8 months [9.4-12.4] in the 531 patients with two to four tumours, and 10.8 months [9.1-12.7] in the 208 patients with five to ten tumours. Overall survival did not differ between the patients with two to four tumours and those with five to ten (HR 0.97, 95% CI 0.81-1.18 [less than non-inferiority margin], $p=0.78$; non-inferiority <0.0001). Stereotactic radiosurgery-induced adverse events occurred in 101 (8%) patients; nine (2%) patients with one tumour had one or more grade 3-4 event compared with 13 (2%) patients with two to four tumours and six (3%) patients with five to ten tumours. The proportion of patients who had one or more treatment-related adverse event of any grade did not differ significantly between the two groups of patients with multiple tumours (50 [9%] patients with two to four tumours vs 18 [9%] with five to ten; $p=0.89$). Four patients died, mainly of complications relating to stereotactic radiosurgery (two with one tumour and one each in the other two groups). **INTERPRETATION:** Our results suggest that stereotactic radiosurgery without WBRT in patients with five to ten brain metastases is non-inferior to that in patients with two to four brain metastases. Considering the minimal invasiveness of stereotactic radiosurgery and the fewer side-effects than with WBRT, stereotactic radiosurgery might be a suitable alternative for patients with up to ten brain metastases. **FUNDING:** Japan Brain Foundation.

[305] Significance of histology in determining management of lesions regrowing after radiosurgery.

Journal of neuro-oncology. 2014;117(2):303-10
Nath SK, Sheridan AD, Rauch PJ, Yu JB, Minja FJ, Vortmeyer AO, Chiang VL
PMID: 24504499 DOI: 10.1007/s11060-014-1389-2
Brain metastases treated with stereotactic radiosurgery may show delayed enlargement on post-treatment imaging that is of ambiguous etiology. Histopathologic interpretation of brain specimens is often challenging due to the presence of significant radiation effects admixed with irradiated residual tumor of indeterminate viability. The purpose of this study was to assess the impact of histologic findings on clinical outcomes following resection of these lesions. Between 2004 and 2010, 690 patients with brain metastases were enrolled in a prospective gamma knife data repository, and lesions requiring excision were identified. Tissue specimens were divided into four groups based on the ratio of treatment related inflammatory changes (TRIC) to tumor cells, and subsequently patient outcomes were assessed. Of 2,583 metastases treated, 36 were excised due to symptomatic enlargement. Only TRIC, without residual evidence of tumor, was seen in 36% (13/36) of specimens. Resection of these lesions resulted in 100% local control in follow-up. Of the remaining 23 lesions that contained any viable-appearing tumor within the resected specimen, 8 recurred after resection. Lesions that enlarged in the first 6 months were more likely to contain higher amounts of residual tumor cells. Patients with even $<2\%$ tumor cells on excision

had significantly worse local control (75 vs. 100 %, $p = 0.024$) and survival (HR 0.27, $p = 0.029$) compared with those patients with exclusively TRIC. In summary, our findings underscore the importance of surgically obtaining tissue in a method that facilitates complete lesional interpretive histology in order to accurately guide ongoing patient management.

[306] Prognostic factors for stereotactic radiosurgery-treated patients with cerebral metastasis: implications on randomised control trial design and inter-institutional collaboration.

European journal of cancer (Oxford, England : 1990). 2014;50(6):1148-58
Gonda DD, Kim TE, Goetsch SJ, Kawabe T, Watanabe S, Alksne JF, Hattangadi JA, Nitta M, Ott K, Hodgens DW, Carter BS, Yamamoto M, Chen CC
PMID: 24529832 DOI: 10.1016/j.ejca.2014.01.001

INTRODUCTION: Defining key prognostic factors for patients with cerebral metastases who underwent stereotactic radiosurgery (SRS) treatment will greatly facilitate future clinical trial designs. **METHODS:** We adopted a two-phase study design where results from one cohort were validated in a second independent cohort. The exploratory analysis reviewed the survival outcomes of 1017 consecutive patients (with 3610 metastases) who underwent Gamma radiosurgery at the University of California, San Diego (UCSD)/San Diego Gamma Knife Center (SDGKC). Multivariate analysis was performed to identify prognostic factors. Results were validated using data derived from 2519 consecutive patients (with 17,498 metastases) treated with SRS at the Katsuta Hospital. **RESULTS:** For the SDGKC cohort, the median overall survival of patients following SRS was 7 months. Two year follow-up data were available for 85% of the patients. Multivariate analysis found that patient age, Karnofsky Performance Status, systemic cancer status, tumour histology, number of metastasis and cumulative tumour volume independently associated with overall survival ($p < 0.001$). All statistical associations were validated by multivariate analysis of data derived from the Katsuta Hospital cohort. **CONCLUSIONS:** This is the first integrated study that defined prognostic factors for SRS-treated patients with cerebral metastases using an inter-institutional validation study design. The work establishes a model for collaborative interactions between large volume centers and provides prognostic variables that should be incorporated into future clinical trial design.

[307] Intracranial hemangiopericytoma—our experience in 30 years: a series of 43 cases and review of the literature.

World neurosurgery. 2014;81(3-4):556-62
Melone AG, D'Elia A, Santoro F, Salvati M, Delfini R, Cantore G, Santoro A
PMID: 24239740 DOI: 10.1016/j.wneu.2013.11.009

OBJECTIVE: Meningeal hemangiopericytoma (HPC) is a rare, aggressive central nervous system tumor that tends to invade locally and to metastasize, and has a high rate of recurrence. **METHODS:** This study presents a retrospective review of patients managed for intracranial HPC at Rome University Hospital. **RESULTS:** A total of 43 patients with intracranial HPC were treated from 1980 to 2010. Treatment and follow-up information was available for analysis on 36 patients. The median survival for all patients was 83.5 months after date of diagnosis, with 1-year, 5-year, and 10-year survival rates of 100%, 94.4%, and 72.2%, respectively. Eighteen patients (41.86%) had HPC recurrence. The median time until recurrence was 72.24 months, with 1-year, 5-year, and 10-year progression-free survival rates of 98%, 51%, and 29%, respectively. Five patients (11.62%) developed extracranial metastasis. Patients undergoing any form of adjuvant radiation treatment, including external beam radiotherapy, Gamma Knife radiosurgery, and/or proton beam therapy, had no longer median overall survival (OS) (178 vs. 154 months, respectively; $P = .2$); but did have a significantly improved recurrence-free interval (108 vs. 64 months; $P = .04$) compared with patients who did not undergo radiation treatment. Tumor characteristics associated with earlier recurrence included size ≥ 7 cm (log-rank, $P < .05$) and sinus invasion (log-rank, $P < .05$). **CONCLUSIONS:** Strategies combining adjuvant radiation with tumor resection seemed to hinder tumor progression, but had no effect on OS or the development of metastases. Greater extent of resection was associated with

increased OS (log-rank, $P < .05$). Anaplastic HPC was associated with reduced OS and with reduced recurrence interval (log-rank, $P < .05$).

[308] Local control and toxicity outcomes in brainstem metastases treated with single fraction radiosurgery: is there a volume threshold for toxicity?

Journal of neuro-oncology. 2014;117(1):167-74
Kilburn JM, Ellis TL, Lovato JF, Urbanic JJ, Bourland JD, Munley MT, Deguzman AF, McMullen KP, Shaw EG, Tatter SB, Chan MD
PMID: 24504497 DOI: 10.1007/s11060-014-1373-x

Gamma Knife Radiosurgery (GKRS) has been reported in the treatment of brainstem metastases while dose volume toxicity thresholds remain mostly undefined. A retrospective review of 52 brainstem metastases in 44 patients treated with GKRS was completed. A median dose of 18 Gy (range 10-22 Gy) was prescribed to the tumor margin (median 50 % isodose). 25 patients had undergone previous whole brain radiation therapy. Toxicity was graded by the LENT-SOMA scale. Mean and median follow-up was 10 and 6 months. Only 3 of the 44 patients are living. Multiple brain metastases were treated in 75 % of patients. Median size of lesions was 0.134 cc, (range 0.013-6.600 cc). Overall survival rate at 1 year was 32 % (95 % CI 5.0-20.1 %) with a median survival time of 6 months (95 % CI 5.0-16.5). Local control rate at 6 months and 1 year was 88 % (95 % CI 70-95 %) and 74 % (95 % CI 52-87 %). Cause of death was neurologic in 17 patients, non-neurologic in 20 patients, and unknown in four. Four patients experienced treatment related toxicities. Univariate analysis of tumor volume revealed that volume greater than 1.0 cc predicted for toxicity. A strategy of using lower marginal doses with GKRS to brain stem metastases appears to lead to a lower local control rate than seen with lesions treated within the standard dose range in other locations. Tumor size greater than 1.0 cc predicted for treatment-related toxicity.

[309] Stereotactic radiotherapy for large solitary brain metastases.

Cancer radiotherapie : journal de la Societe francaise de radiotherapie oncologique. 2014;18(2):97-106
Feuvert L, Vinchon S, Martin V, Lamprogrou I, Halley A, Calugaru V, Chea M, Valery CA, Simon JM, Mazon JJ
PMID: 24439342 DOI: 10.1016/j.canrad.2013.12.003

PURPOSE: To assess effectiveness and toxicity levels of stereotactic radiation therapy without whole brain radiation therapy in patients with solitary brain metastases larger than 3cm. **PATIENTS AND METHODS:** Between June 2007 and March 2009, 12 patients received fractionated stereotactic radiation therapy and 24 patients underwent stereotactic radiosurgery. For the fractionated stereotactic radiation therapy group, 3x7.7Gy were delivered to the planning target volume (PTV); median volume and diameter were 29.4 cm³ and 4.4cm, respectively. For the stereotactic radiosurgery group, 14Gy were delivered to the PTV; median volume and diameter were 15.6 cm³ and 3.7cm, respectively. **RESULTS:** Median follow-up was 218 days. For the fractionated stereotactic radiation therapy group, local control rates were 100% at 360 days and 64% at 720 days; for the stereotactic radiosurgery group, rates were 58% at 360 days and 48% at 720 days ($P=0.06$). Median survival time was 504 days for the fractionated stereotactic radiation therapy group and 164 days for the stereotactic radiosurgery group ($P=0.049$). Two cases of grade 2 toxicity were observed in the fractionated stereotactic radiation therapy group, and 6 cases of grade 1-2 toxicity, in the stereotactic radiosurgery group. **CONCLUSIONS:** This study provides data to support that fractionated stereotactic radiation therapy without whole brain radiation therapy with a margin dose of 3 fractions of 7.7Gy for treatment of solitary large brain metastases is efficient and well-tolerated. Because of the significant improvement in overall survival, this schedule should be assessed in a randomized trial.

[310] Clinical and economic outcomes of patients with brain metastases based on symptoms: an argument for routine brain screening of those treated with upfront radiosurgery.

Cancer. 2014;120(3):433-41

Lester SC, Taksler GB, Kuremsky JG, Lucas JT Jr, Ayala-Peacock DN, Randolph DM 2nd, Bourland JD, Laxton AW, Tatter SB, Chan MD
PMID: 24452675 DOI: 10.1002/cncr.28422

BACKGROUND: Insurers have started to deny reimbursement for routine brain surveillance with magnetic resonance imaging (MRI) after stereotactic radiosurgery (SRS) for brain metastases in favor of symptom-prompted imaging. The authors investigated the clinical and economic impact of symptomatic versus asymptomatic metastases and related these findings to the use of routine brain surveillance. **METHODS:** Between January 2000 and December 2010, 442 patients underwent upfront SRS for brain metastases. In total, 127 asymptomatic patients and 315 symptomatic patients were included. Medical records were used to determine the presenting symptoms, distant and local brain failure, retreatment, and need for hospital and rehabilitative care. Cost-of-care estimates were based on Medicare payment rates as of January 2013. **RESULTS:** Symptomatic patients had an increased hazard for all-cause mortality (hazard ratio, 1.448) and were more likely to experience neurologic death (42% vs 20%; $P < .0001$). Relative to asymptomatic patients, symptomatic patients required more craniotomies (43% vs 5%; $P < .0001$), had more prolonged hospitalization (2 vs 0 days; $P < .0001$), were more likely to have Radiation Therapy Oncology Group grade 3 and 4 post-treatment symptoms (24% vs 5%; $P < .0001$), and required \$11,957 more on average to manage per patient. Accounting for all-cause mortality rates and the probability of diagnosis at each follow-up period, the authors estimated that insurers would save an average \$1326 per patient by covering routine surveillance MRI after SRS to detect asymptomatic metastases. **CONCLUSIONS:** Patients who presented with symptomatic brain metastases had worse clinical outcomes and cost more to manage than asymptomatic patients. The current findings argue that routine brain surveillance after radiosurgery has clinical benefits and reduces the cost of care.

[311] The accuracy of predicting survival in individual patients with cancer.

Journal of neurosurgery. 2014;120(1):24-30

Kondziolka D, Parry PV, Lunsford LD, Kano H, Flickinger JC, Raskal S, Arai Y, Loeffler JS, Rush S, Knisely JP, Sheehan J, Friedman W, Tarhini AA, Francis L, Lieberman F, Ahluwalia MS, Linskey ME, McDermott M, Sperduto P, Stupp R
PMID: 24160479 DOI: 10.3171/2013.9.JNS13788

OBJECT: Estimating survival time in cancer patients is crucial for clinicians, patients, families, and payers. To provide appropriate and cost-effective care, various data sources are used to provide rational, reliable, and reproducible estimates. The accuracy of such estimates is unknown. **METHODS:** The authors prospectively estimated survival in 150 consecutive cancer patients (median age 62 years) with brain metastases undergoing radiosurgery. They recorded cancer type, number of brain metastases, neurological presentation, extracranial disease status, Karnofsky Performance Scale score, Recursive Partitioning Analysis class, prior whole-brain radiotherapy, and synchronous or metachronous presentation. Finally, the authors asked 18 medical, radiation, or surgical oncologists to predict survival from the time of treatment. **RESULTS:** The actual median patient survival was 10.3 months (95% CI 6.4-14). The median physician-predicted survival was 9.7 months (neurosurgeons = 11.8 months, radiation oncologists = 11.0 months, and medical oncologist = 7.2 months). For patients who died before 10 months, both neurosurgeons and radiation oncologists generally predicted survivals that were more optimistic and medical oncologists that were less so, although no group could accurately predict survivors alive at 14 months. All physicians had individual patient survival predictions that were incorrect by as much as 12-18 months, and 14 of 18 physicians had individual predictions that were in error by more than 18 months. Of the 2700 predictions, 1226 (45%) were off by more than 6 months and 488 (18%) were off by more than 12 months. **CONCLUSIONS:** Although crucial, predicting the survival of cancer patients is difficult. In this study all physicians were unable to accurately predict longer-term survivors. Despite valuable clinical data and predictive scoring techniques, brain and systemic management often led to patient survivals well beyond estimated survivals.

[312] Large intracranial metastatic tumors treated by Gamma Knife surgery: outcomes and prognostic factors.

Journal of neurosurgery. 2014;120(1):52-9

Lee CC, Yen CP, Xu Z, Schlesinger D, Sheehan J
PMID: 24160478 DOI: 10.3171/2013.9.JNS131163

OBJECT: The use of radiosurgery has been well accepted for treating small to medium-size metastatic brain tumors (MBTs). However, its utility in treating large MBTs remains uncertain due to potentially unfavorable effects such as progressive perifocal brain edema and neurological deterioration. In this retrospective study the authors evaluated the local tumor control rate and analyzed possible factors affecting tumor and brain edema response. **METHODS:** The authors defined a large brain metastasis as one with a measurement of 3 cm or more in at least one of the 3 cardinal planes (coronal, axial, or sagittal). A consecutive series of 109 patients with 119 large intracranial metastatic lesions were treated with Gamma Knife surgery (GKS) between October 2000 and December 2012; the median tumor volume was 16.8 cm³ (range 6.0-74.8 cm³). The pre-GKS Karnofsky Performance Status (KPS) score for these patients ranged from 70 to 100. The most common tumors of origin were non-small cell lung cancers (29.4% of cases in this series). Thirty-six patients (33.0%) had previously undergone a craniotomy (1-3 times) for tumor resection. Forty-three patients (39.4%) underwent whole-brain radiotherapy (WBRT) before GKS. Patients were treated with GKS and followed clinically and radiographically at 2- to 3-month intervals thereafter.

RESULTS: The median duration of imaging follow-up after GKS for patients with large MBTs in this series was 6.3 months. In the first follow-up MRI studies (performed within 3 months after GKS), 77 lesions (64.7%) had regressed, 24 (20.2%) were stable, and 18 (15.1%) were found to have grown. Peritumoral brain edema as defined on T2-weighted MRI sequences had decreased in 79 lesions (66.4%), was stable in 21 (17.6%), but had progressed in 19 (16.0%). In the group of patients who survived longer than 6 months (76 patients with 77 MBTs), 88.3% of the MBTs (68 of 77 lesions) had regressed or remained stable at the most recent imaging follow-up, and 89.6% (69 of 77 lesions) showed regression of perifocal brain edema volume or stable condition. The median duration of survival after GKS was 8.3 months for patients with large MBTs. Patients with small cell lung cancer and no previous WBRT had a significantly higher tumor control rate as well as better brain edema relief. Patients with a single metastasis, better KPS scores, and no previous radiosurgery or WBRT were more likely to decrease corticosteroid use after GKS. On the other hand, higher pre-GKS KPS score was the only factor that showed a statistically significant association with longer survival. **CONCLUSIONS:** Treating large MBTs using either microsurgery or radiosurgery is a challenge for neurosurgeons. In selected patients with large brain metastases, radiosurgery offered a reasonable local tumor control rate and favorable functional preservation. Exacerbation of underlying edema was rare in this case series. Far more commonly, edema and steroid use were lessened after radiosurgery. Radiosurgery appears to be a reasonable option for some patients with large MBTs.

[313] Salvage radiosurgery for brain metastases: prognostic factors to consider in patient selection.

International journal of radiation oncology, biology, physics. 2014;88(1):137-42

Kurtz G, Zadeh G, Gingras-Hill G, Millar BA, Laperriere NJ, Bernstein M, Jiang H, Menard C, Chung C

PMID: 24331660 DOI: 10.1016/j.ijrobp.2013.10.003

PURPOSE: Stereotactic radiosurgery (SRS) is offered to patients for recurrent brain metastases after prior brain radiation therapy (RT), but few studies have evaluated the efficacy of salvage SRS or factors to consider in selecting patients for this treatment. This study reports overall survival (OS), intracranial progression-free survival (PFS), and local control (LC) after salvage SRS, and factors associated with outcomes. **METHODS AND MATERIALS:** This is a retrospective review of patients treated from 2009 to 2011 with salvage SRS after prior brain RT for brain metastases. Survival from salvage SRS and from initial brain metastases diagnosis (IBMD) was calculated. Univariate and multivariable (MVA) analyses included

age, performance status, recursive partitioning analysis (RPA) class, extracranial disease control, and time from initial RT to salvage SRS. **RESULTS:** There were 106 patients included in the analysis with a median age of 56.9 years (range 32.5-82 years). A median of 2 metastases were treated per patient (range, 1-12) with a median dose of 21 Gy (range, 12-24) prescribed to the 50% isodose. With a median follow-up of 10.5 months (range, 0.1-68.2), LC was 82.8%, 60.1%, and 46.8% at 6 months, 1 year, and 3 years, respectively. Median PFS was 6.2 months (95% confidence interval [CI]=4.9-7.6). Median OS was 11.7 months (95% CI=8.1-13) from salvage SRS, and 22.1 months from IBMD (95% CI=18.4-26.8). On MVA, age ($P=.01$; hazard ratio [HR]=1.04; 95% CI=1.01-1.07), extracranial disease control ($P=.004$; HR=0.46; 95% CI=0.27-0.78), and interval from initial RT to salvage SRS of at least 265 days ($P=.001$; HR=2.46; 95% CI=1.47-4.09) were predictive of OS. **CONCLUSIONS:** This study demonstrates that patients can have durable local control and survival after salvage SRS for recurrent brain metastases. In particular, younger patients with controlled extracranial disease and a durable response to initial brain RT are likely to benefit from salvage SRS.

2013

[314] Predicting tumor control after resection bed radiosurgery of brain metastases.

Neurosurgery. 2013;73(6):1001-6; discussion 1006

Luther N, Kondziolka D, Kano H, Mousavi SH, Engh JA, Niranjan A, Flickinger JC, Lunsford LD

PMID: 24264235 DOI: 10.1227/NEU.0000000000000148

BACKGROUND: Stereotactic radiosurgery (SRS) to the resection bed of a brain metastasis is an important treatment option. **OBJECTIVE:** To identify factors associated with tumor progression after SRS of the resection bed of a brain metastasis and to evaluate patterns of failure for patients who eventually had tumor progression. **METHODS:** We performed a retrospective analysis of 120 patients who underwent tumor bed radiosurgery after an initial gross total resection. The mean imaging follow-up time was 55 weeks. The median margin dose was 16 Gy. Forty-seven patients (39.2%) underwent whole-brain radiation therapy before or shortly after SRS. **RESULTS:** Local tumor control was achieved in 103 patients (85.8%). Progression-free survival was 96% at 6 months, 87% at 12 months, and 74% at 24 months. Recurrence most commonly occurred deep in the cavity (65%) outside the planned treatment volume (PTV) margin (53%). PTV, cavity diameter, and a margin dose < 16 Gy significantly correlated with local failure. For patients with PTVs ≥ 8.0 cm, local progression-free survival declined to 93% at 6 months, 83% at 12 months, and 65% at 24 months. Development or progression of distant metastases occurred in 40% of patients. Whole-brain radiation therapy was not associated with improved local control. **CONCLUSION:** Resection bed SRS for brain metastases provided excellent local control. The cavity PTV is predictive of tumor control. Because failure usually occurs outside the PTV, inclusion of a judicious 2- to 3-mm margin beyond the area of postoperative enhancement may be prudent.

[315] Brain metastasis from hepatocellular carcinoma: the role of surgery as a prognostic factor.

BMC cancer. 2013;13:567

Han MS, Moon KS, Lee KH, Cho SB, Lim SH, Jang WY, Jung TY, Kim IY, Jung S

PMID: 24289477 DOI: 10.1186/1471-2407-13-567

BACKGROUND: The incidence of brain metastasis from hepatocellular carcinoma (HCC) is expected to increase as a result of prolonged survival due to the recent advances in HCC treatment. However, there is no definite treatment strategy for brain metastasis from HCC mainly due to its rarity and dismal prognosis. To provide helpful recommendations in treatment of brain metastasis from HCC, the authors aimed to identify prognostic factors that influence survival rates with

a review of the recently published data. **METHODS:** Thirty-three cases of brain metastasis, whose incidence was 0.65%, were selected from a total of 5015 HCC patients and reviewed retrospectively in terms of clinical and radiological features. **RESULTS:** Median overall survival time after diagnosis of brain metastasis was 10.4 weeks (95% confidence interval [CI], 5.1-15.7 weeks) with 1-, 6- and 12-month survival rates, of 79%, 24% and 6%, respectively. Median survival of the patients treated with surgical resection or surgical resection followed by whole-brain radiation therapy (WBRT) (25.3 weeks; range, 15.8-34.8 weeks) was longer than that of the patients treated with gamma knife surgery (GKS), WBRT, or GKS followed by WBRT (10.4 weeks; range, 7.5-13.3 weeks) as well as that of patients treated with only steroids (1 week; range, 0.0-3.3 weeks) ($p<0.001$). Child-Pugh's classification A group had a longer median survival time than Child-Pugh's classification B or C group (14.4 weeks vs 8.4 weeks, $p=0.038$). RPA class I & II group had also a longer median survival time than RPA class III group did (13.4 weeks vs 2.4 weeks, $p=0.001$). Surgical resection (hazard ratio [HR] 0.23, 95% CI 0.08-0.66, $p=0.006$) and good liver function at the time of brain metastasis (HR 0.25, 95% CI 0.09-0.69, $p=0.007$) were found to be the powerful prognostic factors for favorable survival in the multivariate analysis. In addition, presence of intratumoral hemorrhage was a statistically significant prognostic factor for survival. **CONCLUSION:** Although HCC patients with brain metastasis showed a very dismal prognosis, surgical intervention was shown to lead to relative prolongation of the survival time, especially in those with preserved hepatic function.

[316] Risk of leptomeningeal disease in patients treated with stereotactic radiosurgery targeting the postoperative resection cavity for brain metastases.

International journal of radiation oncology, biology, physics. 2013;87(4):713-8

Atalar B, Modlin LA, Choi CY, Adler JR, Gibbs IC, Chang SD, Harsh GR 4th, Li G, Nagpal S, Hanlon A, Soltys SG

PMID: 24054875 DOI: 10.1016/j.ijrobp.2013.07.034

PURPOSE: We sought to determine the risk of leptomeningeal disease (LMD) in patients treated with stereotactic radiosurgery (SRS) targeting the postsurgical resection cavity of a brain metastasis, deferring whole-brain radiation therapy (WBRT) in all patients. **METHODS AND MATERIALS:** We retrospectively reviewed 175 brain metastasis resection cavities in 165 patients treated from 1998 to 2011 with postoperative SRS. The cumulative incidence rates, with death as a competing risk, of LMD, local failure (LF), and distant brain parenchymal failure (DF) were estimated. Variables associated with LMD were evaluated, including LF, DF, posterior fossa location, resection type (en-bloc vs piecemeal or unknown), and histology (lung, colon, breast, melanoma, gynecologic, other). **RESULTS:** With a median follow-up of 12 months (range, 1-157 months), median overall survival was 17 months. Twenty-one of 165 patients (13%) developed LMD at a median of 5 months (range, 2-33 months) following SRS. The 1-year cumulative incidence rates, with death as a competing risk, were 10% (95% confidence interval [CI], 6%-15%) for developing LF, 54% (95% CI, 46%-61%) for DF, and 11% (95% CI, 7%-17%) for LMD. On univariate analysis, only breast cancer histology (hazard ratio, 2.96) was associated with an increased risk of LMD. The 1-year cumulative incidence of LMD was 24% (95% CI, 9%-41%) for breast cancer compared to 9% (95% CI, 5%-14%) for non-breast histology ($P=.004$). **CONCLUSIONS:** In patients treated with SRS targeting the postoperative cavity following resection, those with breast cancer histology were at higher risk of LMD. It is unknown whether the inclusion of whole-brain irradiation or novel strategies such as preresection SRS would improve this risk or if the rate of LMD is inherently higher with breast histology.

[317] Tumor volume as a predictor of survival and local control in patients with brain metastases treated with Gamma Knife surgery.

Journal of neurosurgery. 2013;119(5):1139-44

Baschnagel AM, Meyer KD, Chen PY, Krauss DJ, Olson RE, Pieper DR, Maitz AH, Ye H, Grills IS

PMID: 23971958 DOI: 10.3171/2013.7.JNS13431

OBJECT: The aim of this study was to examine tumor volume as a prognostic

factor for patients with brain metastases treated with Gamma Knife surgery (GKS). **METHODS:** Two hundred fifty patients with 1-14 brain metastases who had initially undergone GKS alone at a single institution were retrospectively reviewed. Patients who received upfront whole brain radiation therapy were excluded. Survival times were estimated using the Kaplan-Meier method. Univariate and multivariate analyses using Cox proportional hazard regression models were used to determine if various prognostic factors could predict overall survival, distant brain failure, and local control. **RESULTS:** Median overall survival was 7.1 months and the 1-year local control rate was 91.5%. Median time to distant brain failure was 8.0 months. On univariate analysis an increasing total tumor volume was significantly associated with worse survival ($p = 0.031$) whereas the number of brain metastases, analyzed as a continuous variable, was not ($p = 0.082$). After adjusting for age, Karnofsky Performance Scale score, and extracranial disease on multivariate analysis, total tumor volume was found to be a better predictor of overall survival ($p = 0.046$) than number of brain metastases analyzed as a continuous variable ($p = 0.098$). A total tumor volume cutoff value of ≥ 2 cm³ ($p = 0.008$) was a stronger predictor of overall survival than the number of brain metastases ($p = 0.098$). Larger tumor volume and extracranial disease, but not the number of brain metastases, were predictive of distant brain failure on multivariate analysis. Local tumor control at 1 year was 97% for lesions < 2 cm³ compared with 75% for lesions ≥ 2 cm³ ($p < 0.001$). **CONCLUSIONS:** After adjusting for other factors, a total brain metastasis volume was a strong and independent predictor for overall survival, distant brain failure, and local control, even when considering the number of metastases.

[318] Gamma knife radiosurgery for brain metastases from breast cancer.

Journal of Korean Neurological Society. 2013;54(5):399-404

Jo KI, Im YH, Kong DS, Seol HJ, Nam DH, Lee JI

PMID: 24379946 DOI: 10.3340/jkns.2013.54.5.399

OBJECTIVE: The authors conducted a retrospective cohort study to determine prognostic factors and treatment outcomes of brain metastases (BM) from breast cancer (BC) after Gamma Knife radiosurgery (GKS). **METHODS:** Pathologic and clinical features, and outcomes were analyzed in a cohort of 62 patients with BM from BC treated by GKS. The Kaplan-Meier method, the log-rank test, and Cox's proportional hazards model were used to assess prognostic factors. **RESULTS:** Median survival after GKS was 73.0 weeks (95% confidence interval, 46.0-100.1). HER2+ [hazard ratio (HR) 0.441; $p=0.045$], Karnofsky performance scale (KPS) ≥ 70 (RR 0.416; $p=0.050$) and systemic chemotherapy after GKS (RR 0.282; $p=0.001$) were found to be a favorable prognostic factor of overall survival. Actuarial local control (LC) rate were 89.5 \pm 4.5% and 70.5 \pm 6.9% at 6 and 12 months after GKS, respectively. No prognostic factors were found to affect LC rate. Uni- and multivariate analysis revealed that the distant control (DC) rate was higher in patients with; a small number (≤ 3) of metastasis (HR 0.300; $p=0.045$), no known extracranial metastasis ($p=0.013$, log-rank test), or the HER2+ subtype (HR 0.267; $p=0.027$). Additional whole brain radiation therapy and metastasis volume were not found to be significantly associated with LC, DC, or overall survival. **CONCLUSION:** The treatment outcomes of patients with newly diagnosed BM from BC treated with GKS could be affected primarily by intrinsic subtype, KPS, and systemic chemotherapy. Therapeutic strategy and prognosis scoring system should be individualized based on considerations of intrinsic subtype in addition to traditionally known parameters related to stereotactic radiosurgery.

[319] Gamma Knife radiosurgery in the management of brainstem metastases.

Clinical neurology and neurosurgery. 2013;115(10):2023-8

Jung EW, Rakowski JT, Delly F, Jagannathan J, Konski AA, Guthikonda M, Kim H, Mittal S

PMID: 23870233 DOI: 10.1016/j.clineuro.2013.06.012

BACKGROUND: Metastases to the brainstem portend a poor prognosis and present a challenge in clinical management. Surgical resection is rarely a viable option. **METHODS:** Post-treatment MRI scans of patients with brainstem

metastases treated with radiosurgery were used to determine local control and disease progression. Median survival was calculated using Kaplan-Meier analysis. Univariate and multivariate analyses were performed using log-rank test and Cox proportional hazards model, respectively. **RESULTS:** Thirty-two consecutive patients with brainstem metastasis underwent Gamma Knife radiosurgery. Median age was 50 years. Median tumor volume was 0.71 cm³ and median tumor margin dose was 13 Gy. Seventeen of 32 patients received WBRT prior to stereotactic radiosurgery. Median survival was 5.2 months. There was a statistically significant difference in survival based on RTOG recursive partition analysis (RPA) class. Median survival of patients categorized as RPA class I was 19.2 months, RPA class II was 8.4 months, and RPA class III was 1.9 months. The overall local tumor control rate was 87.5%. There were no acute complications following stereotactic radiosurgery and no evidence of radiation necrosis noted on post-treatment MRI scans. **CONCLUSION:** Stereotactic radiosurgery is an effective treatment for brainstem metastases and should be considered especially for patients with good performance status.

[320] Risk of seizure and its clinical implication in the patients with cerebral metastasis from lung cancer.

Acta neurochirurgica. 2013;155(10):1833-7

Lee MH, Kong DS, Seol HJ, Nam DH, Lee JI

PMID: 23982228 DOI: 10.1007/s00701-013-1826-6

BACKGROUND: The prevalence, risk factors, and clinical implication of seizure development were investigated in patients with metastatic brain tumors. **METHODS:** Medical records and radiological findings were analyzed retrospectively in 258 patients with brain metastasis from lung cancer who underwent Gamma Knife radiosurgery (GKS) between January 2008 and December 2009. **RESULTS:** During the follow-up period 32 patients (12.4 %) experienced seizure episodes. Coexistence of leptomeningeal seeding was a significant risk factor related to development of seizure ($p < 0.001$). Prophylactic use of anticonvulsants was not correlated with reduction of seizure incidence ($p = 0.818$). Continued use of anticonvulsants was necessary in nine of the 258 patients (3.5 %) because of recurrent seizures. Imaging studies performed immediately after seizure attacks in the patients with known metastatic brain lesions revealed tumor progression or complications related to treatment in 35 of 42 episodes of seizure (77.8 %). **CONCLUSIONS:** Patients with metastatic lesions have a substantial risk of developing seizure. Seizure in known metastatic brain tumor patients are usually related to disease progression or complications of treatment. Follow-up imaging should be considered for each seizure episode and adequate multimodal treatment needs to be added to antiepileptic medication.

[321] Tumor histology predicts patterns of failure and survival in patients with brain metastases from lung cancer treated with gamma knife radiosurgery.

Neurosurgery. 2013;73(4):641-7; discussion 647

Kuremsky JG, Urbanic JJ, Petty WJ, Lovato JF, Bourland JD, Tatter SB, Ellis TL, McMullen KP, Shaw EG, Chan MD

PMID: 23842552 DOI: 10.1227/NEU.0000000000000072

BACKGROUND: We review our experience with lung cancer patients with newly diagnosed brain metastases treated with Gamma Knife radiosurgery (GKRS).

OBJECTIVE: To determine whether tumor histology predicts patient outcomes. **METHODS:** Between July 1, 2000, and December 31, 2010, 271 patients with brain metastases from primary lung cancer were treated with GKRS at our institution. Included in our study were 44 squamous cell carcinoma (SCC), 31 small cell carcinoma (SCLC), and 138 adenocarcinoma (ACA) patients; 47 patients with insufficient pathology to determine subtype were excluded. No non-small cell lung cancer (NSCLC) patients received whole-brain radiation therapy (WBRT) before their GKRS, and SCLC patients were allowed to have prophylactic cranial irradiation, but no previously known brain metastases. A median of 2 lesions were treated per patient with median marginal dose of 20 Gy. **RESULTS:** Median survival was 10.2 months for ACA, 5.9 months for SCLC, and 5.3 months for SCC patients ($P = .008$). The 1-year local control rates were 86%, 86%, and 54% for

ACA, SCC, and SCLC, respectively (P = .027). The 1-year distant failure rates were 35%, 63%, and 65% for ACA, SCC, and SCLC, respectively (P = .057). The likelihood of dying of neurological death was 29%, 36%, and 55% for ACA, SCC, and SCLC, respectively (P = .027). The median time to WBRT was 11 months for SCC and 24 months for ACA patients (P = .04). Multivariate analysis confirmed SCLC histology as a significant predictor of worsened local control (hazard ratio [HR]: 6.46, P = .025) and distant failure (HR: 3.32, P = .0027). For NSCLC histologies, SCC predicted for earlier time to salvage WBRT (HR: 2.552, P = .01) and worsened overall survival (HR: 1.77, P < .0121). **CONCLUSION:** Histological subtype of lung cancer appears to predict outcomes. Future trials and prognostic indices should take these histology-specific patterns into account.

[322] Treatment Options of Metastatic Brain Tumors from Hepatocellular Carcinoma: Surgical Resection vs. Gamma Knife Radiosurgery vs. Whole Brain Radiation Therapy.

Brain tumor research and treatment. 2013;1(2):78-84
Park TY, Na YC, Lee WH, Kim JH, Chang WS, Jung HH, Chang JH, Chang JW, Park YG
PMID: 24904896 DOI: 10.14791/btrt.2013.1.2.78

OBJECTIVE: Although metastasis of hepatocellular carcinoma to the brain is uncommon, it is associated with a very high mortality rate and most patients usually expire within 1 year after brain metastasis. The aim of this study is to identify the effectiveness of the active interventions such as gamma knife radiosurgery or surgical intervention for these patients. **METHODS:** We retrospectively reviewed the medical records and imaging data of 59 patients with metastatic brain tumors from hepatocellular carcinoma from May 2004 to September 2012. The study included patients with available clinical and radiological data who had been diagnosed with metastatic hepatocellular carcinoma of the brain, confirmed by magnetic resonance imaging. The overall survival time was analyzed and compared according to each risk factor. **RESULTS:** The mean age at diagnosis of metastatic brain tumor was 52.2 years (14-77). The mean follow-up duration was 13.3 weeks (0.1-117.6). Overall median survival was 4.3 weeks (95% confidence interval, 2.2-6.4). The results from an analysis of clinical factors related to survival revealed that treatment modalities were significantly related to the patient's survival (log rank, p=0.006). Twenty patients (32.8%) experienced tumor bleeding, and the survival time of the patients with tumor bleeding tended to be shorter, although the result was not statistically significant (log rank, p=0.058). Hepatic reserve, by Child-Pugh classification, was grade A in 38 patients (64.4%), grade B in 16 patients (27.1%), and grade C in 5 patients (8.5%), and was significantly related to the patient's survival (log rank, p=0.000). **CONCLUSION:** Although patients with metastatic brain tumors from hepatocellular carcinoma showed poor survival, active intervention including surgical resection or gamma knife radiosurgery may result in better survival, especially if patients have preserved liver function.

[323] Clinical outcome in gamma knife radiosurgery for metastatic brain tumors from the primary breast cancer : prognostic factors in local treatment failure and survival.

Journal of Korean Neurosurgical Society. 2013;54(4):329-35
Choi SW, Kwon DH, Kim CJ
PMID: 24294457 DOI: 10.3340/jkns.2013.54.4.329

OBJECTIVE: Brain metastases in primary breast cancer patients are considerable sources of morbidity and mortality. Gamma knife radiosurgery (GKRS) has gained popularity as an up-front therapy in treating such metastases over traditional radiation therapy due to better neurocognitive function preservation. The aim of this study was to clarify the prognostic factors for local tumor control and survival in radiosurgery for brain metastases from primary breast cancer. **METHODS:** From March 2001 to May 2011, 124 women with metastatic brain lesions originating from a primary breast cancer underwent GKRS at a tertiary medical center in Seoul, Korea. All patients had radiosurgery as a primary treatment or salvage therapy. We retrospectively reviewed their clinical outcomes and radiological responses. The end point of this study was the date of patient's death or the last

follow-up examination. **RESULTS:** In total, 106 patients (268 lesions) were available for follow-up imaging. The median follow-up time was 7.5 months. The mean treated tumor volume at the time of GKRS was 6273 mm³ (range, 4.5-27745 mm³) and the median dose delivered to the tumor margin was 22 Gy (range, 20-25 Gy). Local recurrence was assessed in 86 patients (216 lesions) and found to have occurred in 36 patients (83 lesions, 38.6%) with a median time of 6 months (range, 4-16 months). A treated tumor volume >5000 mm³ was significantly correlated with poor local tumor control through a multivariate analysis (hazard risk=7.091, p=0.01). Overall survival was 79.9%, 48.3%, and 15.3% at 6, 12, and 24 months, respectively. The median overall survival was 11 months after GKRS (range, 6 days-113 months). Multivariate analysis showed that the pre-GKRS Karnofsky performance status, leptomeningeal seeding prior to initial GKRS, and multiple metastatic lesions were significant prognostic factors for reduced overall survival (hazard risk=1.94, p=0.001, hazard risk=7.13, p<0.001, and hazard risk=1.46, p=0.046, respectively). **CONCLUSION:** GKRS has shown to be an effective and safe treatment modality for treating brain metastases of primary breast cancer. Most metastatic brain lesions initially respond to GKRS, though, many patients have further CNS progression in subsequent periods. Patients with poor Karnofsky performance status and multiple metastatic lesions are at risk of CNS progression and poor survival, and a more frequent and strict surveillance protocol is suggested in such high-risk groups.

[324] Survival and intracranial control of patients with 5 or more brain metastases treated with gamma knife stereotactic radiosurgery.

American journal of clinical oncology. 2013;36(5):486-90
Raldow AC, Chiang VL, Knisely JP, Yu JB
PMID: 22706180 DOI: 10.1097/COC.0b013e31825494ef

PURPOSE: Limited data are available to help inform decisions about stereotactic radiosurgery for patients with ≥5 brain metastases. We therefore performed a retrospective analysis of patients treated for >5 brain metastases. **MATERIALS/ METHODS:** Patients who underwent treatment for ≥5 brain metastases from October 2000 to September 2010 were identified. Overall survival (OS) for each patient was calculated from the date of first treatment of ≥5 brain metastases. Intracranial recurrence-free survival was defined when posttreatment magnetic resonance imaging showed evidence for disease progression. Cox proportional hazards regression was performed for OS and intracranial recurrence free survival. Variables included sex, age, Karnofsky Performance Status (KPS), histology, prior whole-brain radiation treatment or Gamma Knife treatment, and number of metastases treated. **RESULTS:** A total of 103 patients were identified. Median OS was 8.3 months. Median OS was 7.6 months and 8.3 months, for patients with 5 to 9 and ≥10 metastases, respectively. KPS was the only significant variable affecting OS (P <0.01). Forty-six patients had post-Gamma Knife surveillance imaging recorded. There was a trend towards a higher hazard for intracranial failure for patients with 10+ versus 5 to 9 metastases, however, the association did not reach statistical significance (univariate P=0.09, multivariate P=0.21). **CONCLUSIONS:** OS for carefully selected patients with 5 or more brain metastases treated with stereotactic radiosurgery alone is reasonable and compares well with historical controls. KPS is the most important factor predicting OS.

[325] A clinical model for identifying radiosensitive tumor genotypes in non-small cell lung cancer.

Clinical cancer research : an official journal of the American Association for Cancer Research. 2013;19(19):5523-32
Johung KL, Yao X, Li F, Yu JB, Gettinger SN, Goldberg S, Decker RH, Hess JA, Chiang VL, Contessa JN
PMID: 23897899 DOI: 10.1158/1078-0432.CCR-13-0836

PURPOSE: Non-small cell lung cancer (NSCLC) includes a spectrum of radiosensitive and radioresistant tumors. However, little is known about the molecular determinants of cellular radiation responses. We examined clinical outcomes after gamma knife radiotherapy for NSCLC intracranial metastases to

evaluate the use of this model for determining radiosensitive tumor genotypes. **EXPERIMENTAL DESIGN:** Between 2005 and 2012, 239 patients with NSCLC were enrolled in a prospective gamma knife data repository. Molecular pathology regarding EGF receptor (EGFR), ALK, and KRAS mutation status was available for 81 patients. Local and distant brain control was determined for 79 patients with 469 brain metastases. Modified Cox proportional hazards models were established to evaluate local control for treated lesions after serial gamma knife treatments. **RESULTS:** In total, 11% of patients developed in-field recurrence. No patients with metastases from tumors with EGFR mutations (0/164 lesions) or EML4-ALK translocations (0/61 lesions) recurred in-field. In contrast, 19% of patients without these mutations and 18% of patients with KRAS mutations recurred in-field (10/139 and 3/105 lesions, respectively). Rates of distant brain recurrence did not significantly differ across tumor genotypes. The predicted median in-field local control was significantly longer for EGFR-mutant and ALK-translocated tumors compared with other patients with NSCLC ($P < 0.001$), whereas distant brain recurrence time was equivalent ($P = 0.97$). On multivariate analysis, EGFR mutation, ALK translocation, and metastasis size were independent predictors for superior local control after gamma knife treatment. **CONCLUSIONS:** This study suggests that EGFR kinase domain mutations and EML4-ALK translocations are radiosensitive NSCLC genotypes, and proposes a novel model to identify radiosensitive subtypes of NSCLC.

[326] Clinical outcome with gamma-knife surgery or surgery for brain metastases from colorectal cancer.

Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2013;20(10):1417-21

Kim HJ, Huh JW, Jung TY, Kim IY, Kim HR, Jung S, Kim YJ
PMID: 23910824 DOI: 10.1016/j.jocn.2012.12.020

The aim of this study was to investigate the clinical outcomes after gamma knife surgery (GKS) or surgery as the first treatment for brain metastases in colorectal cancer (CRC). Of the 4350 patients diagnosed with CRC at our institution identified from 1987 to 2009, 27 patients who underwent GKS (GKS group) and 11 who underwent surgery (surgery group) were included. The oncologic outcomes were compared between the two groups. Local control was significantly better in the surgery group than in the GKS group (90% versus [vs.] 71.4%, respectively; $p=0.006$). The rate of symptom relief after 3 months was significantly higher in the surgery group than in the GKS group (72.7 vs. 18.5%, respectively; $p=0.005$). The median survival after GKS was 5.6 months and surgery was 16.2 months. In multivariate analysis, controlled primary tumor ($p=0.038$) and solitary metastasis ($p=0.028$) were correlated with prolonged overall survival, whereas surgery ($p=0.034$) was associated with longer local control. Surgery for brain metastasis from CRC is more advantageous in local control and neurologic symptom palliation than GSK. In multivariate analysis, overall survival was associated with controlled primary tumor and solitary metastasis.

[327] Stereotactic radiosurgery for brain metastases from hepatocellular carcinoma.

Journal of neuro-oncology. 2013;115(1):45-51

Han JH, Kim DG, Chung HT, Paek SH, Park CK, Kim CY, Kim YH, Jung HW
PMID: 23813231 DOI: 10.1007/s11060-013-1192-5

The purpose of this study is to investigate the possible role of stereotactic radiosurgery (SRS) in the management of patients with brain metastases from hepatocellular carcinoma (HCC). Thirty-two consecutive patients with 80 brain metastases from HCC were treated with SRS. Twenty-eight (87.5%) patients were male, and the mean age of the patients was 54 +/- 12 years (range 22-73). Twenty-seven (84.4%) patients were classified as RTOG RPA Class 2. The mean tumor volume was 6.14 +/- 11.3 cm(3) (range 0.01-67.3). The mean marginal dose prescribed was 20.1 +/- 3.6 Gy (range 10.0-25.0). The median overall survival time after SRS was 11.3 +/- 5.8 weeks (95% CI 0-22.7). A greater total volume of brain metastases (>14 cm(3)) was the only independent prognostic factor (HR = 2.419; 95% CI 1.040-5.624; $p = 0.040$). The actuarial control rate of brain metastases

was 51.3% at 4 months after SRS. The prescribed marginal dose (>18 Gy) was significantly related with the actuarial tumor control (HR = 0.254; 95% CI 0.089-0.725; $p = 0.010$). The prognosis of patients with brain metastases from HCC is dismal even with the modern technology of radiosurgery. The marginal dose prescribed should be reevaluated to improve upon the current poor local control rates.

[328] Gamma knife radiosurgery for resectable brain metastasis.

World neurosurgery. 2013;80(3-4):351-8

Xu Z, Elsharkawy M, Schlesinger D, Sheehan J
PMID: 22484072 DOI: 10.1016/j.wneu.2012.03.021

BACKGROUND: Surgical resection is most often performed for superficially located brain metastasis. We evaluate the use of gamma knife radiosurgery (GKS) for resectable non-small cell lung cancer (NSCLC) brain metastases located <3 cm away from the outer cortical surface. **METHODS:** Between 1999 and 2009, 306 patients were treated for brain metastasis from NSCLC at the University of Virginia. The current study included patients with 3 or fewer resectable brain metastases, with resectable being defined as <3 cm from the nearest outer cortical surface of the brain. Sixty-four patients with 111 metastatic brain lesions were eligible for the study. Survival, tumor control, and need for a craniotomy and tumor resection after GKS were evaluated. **RESULTS:** The mean overall survival rate in this cohort is 13.5 months (median, 8 months) after GKS, and the mean overall survival after diagnosis of the primary lesion was 31.5 months (median, 19 months). Factors related to prolonged survival after GKS were gender, Karnofsky performance score (KPS), recursive partitioning analysis (RPA) class, age at GKS, number of metastatic lesions, development of new intracranial lesions, and number of lobes involved with metastatic disease. The actuarial local tumor control rate was 84% at 6 months. Two patients (3%) underwent a craniotomy and tumor resection for their progressive superficial metastasis after GKS. **CONCLUSIONS:** GKS for NSCLC brain metastases is effective in patients with 3 or fewer resectable tumors. The need for a craniotomy in this subgroup of patients after GKS is very low.

[329] Motor function after stereotactic radiosurgery for brain metastases in the region of the motor cortex.

Journal of neurosurgery. 2013;119(3):683-8

Luther N, Kondziolka D, Kano H, Mousavi SH, Flickinger JC, Lunsford LD
PMID: 23870018 DOI: 10.3171/2013.6.JNS122081

OBJECT: The authors sought to better define the clinical response of patients who underwent stereotactic radiosurgery (SRS) for brain metastases located in the region of the motor cortex. **METHODS:** A retrospective analysis was performed in 2026 patients with brain metastasis who underwent SRS with the Gamma Knife between 2002 and 2012, and multiple factors that affect motor function before and after SRS were evaluated. Ninety-four patients with tumors ≥ 1.5 cm in diameter located in or adjacent to the motor strip were identified, including 2 patients with bilateral motor strip metastases. **RESULTS:** Motor function improved after SRS in 30 (31%) of 96 cases, remained stable in 48 (50%), and worsened over time in 18 (19%) instances. Forty-seven patients had no motor weakness prior to radiosurgery; 10 (22%) developed new Grade 3/5-4/5 weakness. Thirty (68%) of 44 patients with $\geq 3/5$ pre-SRS weakness improved, 6 (14%) remained stable, and 8 (18%) worsened. Three of 5 patients with < 3/5 pre-SRS motor function improved. Motor deficits prior to SRS did not correlate with a worse outcome; however, worse outcomes were associated with larger tumor volumes. The median tumor volume in patients whose function improved or remained stable was 5.3 cm(3), but it was 9.2 cm(3) in patients who worsened ($p < 0.05$). Tumor volumes > 9 cm(3) were associated with a higher risk of worsening motor function. Adverse radiation effects occurred in 5 patients. **CONCLUSIONS:** Most intact patients with brain metastases in or adjacent to motor cortex maintained neurological function after SRS, and most patients with symptomatic motor weakness remained stable or improved. Larger tumor volumes were associated with less satisfactory outcomes.

[330] Survival among patients with 10 or more brain metastases treated with stereotactic radiosurgery.

Journal of neurosurgery. 2013;119(2):457-62

Rava P, Leonard K, Sioshansi S, Curran B, Wazer DE, Cosgrove GR, Noren G, Hepel JT

PMID: 23662828 DOI: 10.3171/2013.4.JNS121751

OBJECT: The goal of this study was to evaluate outcomes in patients with ≥ 10 CNS metastases treated with Gamma Knife stereotactic radiosurgery (GK-SRS).

METHODS: Patients with ≥ 10 brain metastases treated using GK-SRS during the period between 2004 and 2010 were identified. Overall survival and local and regional control as well as necrosis rates were determined. The influence of age, sex, histological type, extracranial metastases, whole-brain radiation therapy, and number of brain metastases was analyzed using the Kaplan-Meier method. Univariate (log-rank) analyses were performed, with a p value of < 0.05 considered significant. **RESULTS:** Fifty-three patients with ≥ 10 brain metastases were treated between 2004 and 2010. All had a Karnofsky Performance Status score of ≥ 70 . Seventy-two percent had either non-small cell lung cancer (38%) or breast cancer (34%); melanoma, small cell lung cancer, renal cell carcinoma, and testicular, colon, and ovarian cancer contributed the remaining 28%. On average, 10.9 lesions were treated in a single session. Sixty-four percent of patients received prior whole-brain radiation therapy. The median survival was 6.5 months. One-year overall survival was 42% versus 14% when comparing breast cancer and other histological types, respectively ($p = 0.074$). Age, extracranial metastases, number of brain metastases, and previous CNS radiation therapy were not significant prognostic factors. Although the median time to local failure was not reached, the median time to regional failure was 3 months. Female sex was associated with longer time to regional failure ($p = 0.004$), as was breast cancer histological type ($p = 0.089$). No patient experienced symptomatic necrosis.

CONCLUSIONS: Patients with ≥ 10 brain metastases who received prior CNS radiation can safely undergo repeat treatment with GK-SRS. With median survival exceeding 6 months, aggressive local treatment remains an option; however, rapid CNS failure is to be expected. Although numbers are limited, patients with breast cancer represent one group of individuals who would benefit most, with prolonged survival and extended time to CNS recurrence.

[331] The efficacy and limitations of stereotactic radiosurgery as a salvage treatment after failed whole brain radiotherapy for brain metastases.

Journal of neuro-oncology. 2013;113(3):459-65

Yomo S, Hayashi M

PMID: 23661101 DOI: 10.1007/s11060-013-1138-y

The aim of the present study was to evaluate the efficacy and limitations of repeat stereotactic radiosurgery (SRS) salvage for patients with recurrence of brain metastases (BM) after whole brain radiotherapy (WBRT). This is a retrospective, observational, single-center trial analyzing 77 consecutive patients with recurrent BM who were treated primarily with WBRT. All patients underwent SRS as salvage treatment. Median age was 62 years, and median Karnofsky performance status (KPS) was 80. The median interval between the starting date of WBRT and radiosurgery was 10.6 months. One, two and more than two SRS sessions were required in 42, 13 and 22 patients, respectively. The median total planning target volume (PTV) was 8.1 mL and the median dose prescribed was 20 Gy. The median follow-up was 7.7 months. 1- and 2-year neurological death-free survival (NS) rates were 87 and 78 %, respectively. Competing risk analysis demonstrated active extra-central nervous system (CNS) disease [Hazard ratio (HR) 0.236, $P = 0.041$] and total PTV on initial SRS (≥ 5 mL) (HR 4.22, $P = 0.033$) to be associated with the NS rate. 1- and 2-year overall survival (OS) rates were 41 and 11 %, respectively. The median OS time was 8.2 months. Active extra-CNS disease (HR 1.94, $P = 0.034$) and high KPS (≥ 90) (HR 0.409, $P = 0.006$) were associated with the OS rate. In total, 798 tumors (75 %) in 66 patients (86 %) with sufficient radiological follow-up data were evaluated. 1- and 2-year metastasis local control rates were 76.6 and 57.9 %, respectively. Prescribed dose (≥ 20 Gy) (HR 0.326, $P < 0.001$), tumor volume (≥ 2 mL) (HR 1.98, $P = 0.007$) and metastases from breast

cancer (HR 0.435, $P < 0.001$) were independent predictive factors for local tumor control. Repeat salvage SRS for recurrent BM after WBRT appeared to be a safe and effective treatment. In the majority of patients, even those with numerous BM, neurological death could be delayed or even prevented.

[332] Significance of the number of brain metastases for identifying patients who don't need whole brain radiotherapy: implication as oligometastases of the brain.

Journal of radiosurgery and SBRT. 2013;2(2):119-126

Nogi S, Nakayama H, Tajima Y, Okubo M, Mikami R, Kanesaka N, Sugahara S, Tokuyue K

PMID: 29296350 DOI:

BACKGROUND AND PURPOSE: To investigate the significance of the number of brain metastases in the treatment with stereotactic radiotherapy (SRT) with or without whole brain radiotherapy (WBRT). **MATERIAL AND METHODS:** Between February 2003 and October 2010, 218 consecutive patients with brain metastases who underwent SRT alone or WBRT plus SRT were investigated. The prognostic factors affecting overall survival and brain progression-free survival were analyzed by multivariate and univariate analysis. By logistic regression analysis, factors associated with the number recurrences of brain metastasis after SRT were also investigated. **RESULTS:** The median overall and brain progression-free survivals were 7.2 months and 4.3 months, respectively. Significant prognostic factors for overall survival in multivariate analyses were performance status (hazard ratio [HR] = 1.71, 95% confidence interval [CI] 1.13-2.57, $p = 0.01$) and the number of brain metastases (HR = 1.75, 95% CI 1.08-2.83, $p = 0.02$). Cut-off line of the number of brain metastases was between 3 and 4, and 3 or fewer brain metastases were significantly better than 4 or more in prognosis by univariate and multivariate analysis ($p < 0.01$, $p = 0.02$). **CONCLUSIONS:** The patients with 3 or fewer brain metastases were associated with brain progression free survival and 3 or fewer brain relapse. Repeated SRT without WBRT may be effective for patients with 3 or fewer brain metastases.

[333] Gamma knife stereotactic radiosurgery for renal cell carcinoma and melanoma brain metastases-comparison of dose response.

Journal of radiosurgery and SBRT. 2013;2(3):193-207

Lin HY, Watanabe Y, Cho LC, Yuan J, Hunt MA, Sperduto PW, Abosch A, Watts CR, Lee CK

PMID: 29296362 DOI:

BACKGROUND: Metastatic melanoma appears to have inferior local control (LC) than renal cell carcinoma (RCC) after stereotactic radiosurgery (SRS) to the brain. **OBJECTIVE:** To retrospectively examine RCC vs. melanoma LC dose response. **METHODS:** Follow-up data were available for 88 patients (RCC=38; melanoma=50) with 235 tumors (RCC=92; melanoma=143) treated with Gamma Knife SRS between Dec. 2005 to Aug. 2012. LC was compared among RCC vs. melanoma and then at each margin dose (≤ 18 Gy, 20Gy, 22Gy, and 24Gy). Patient survival and toxicity were analyzed. Median follow-up was 9.8 months (RCC) and 5.4 months (melanoma). **RESULTS:** Patient characteristics were similar between RCC vs. melanoma with respect to gender, age, KPS, GPA, lesions per patient, and tumor volume. For all margin doses, LC at 6 months was 98.6% (RCC) vs. 79.2% (melanoma). When broken down by margin dose, at ≤ 18 Gy ($P < 0.0001$) and 20 Gy ($P = 0.02$), RCC had better LC compared to melanoma. At 22 Gy, LC were similar between the two histologies ($P = 0.19$). At 24 Gy, melanoma had better LC than RCC ($P = 0.02$). Tumor volumes were similar between RCC vs. melanoma at each margin dose ($P > 0.05$). Small melanoma tumors (< 4 ml) exhibited LC dose dependence. Median survival was 16.1 months (RCC) and 9.6 months (melanoma). Toxicity was not significantly different between the two histologies and margin doses. **CONCLUSIONS:** RCC has significantly better LC than melanoma after SRS. Higher doses could be used for melanoma tumors < 4 ml to improve melanoma LC.

[334] Gamma knife treatment strategy for metastatic brain tumors.

Acta neurochirurgica. Supplement. 2013;116:63-9

Takakura K, Hayashi M, Chernov MF, Tamura N, Izawa M, Okada Y, Tamura M, Muragaki Y, Iseki H

PMID: 23417461 DOI: 10.1007/978-3-7091-1376-9_11

From 1993 to 2011, a total of 3,095 patients with brain metastases underwent Gamma Knife radiosurgery (GKS) at Tokyo Women's Medical University. Follow-up information on 2,283 of these patients was available for retrospective analysis. The cases were separated into three groups according to the treatment period, the model of the Gamma Knife used, main goals of treatment, and technical nuances of radiosurgery. In the latest cohort of patients treated with the Leksell Gamma Knife model 4C with automatic positioning system, an optimized treatment strategy was applied. It was based on highly selective dose planning, with the use of multiple small isocenters located within the bulk of the mass, which was done for prevention of the excessive irradiation of the perilesional brain and avoidance of its posttreatment edema. In cases of large cystic tumors, selective coverage of the contrast-enhancing capsule with chain-like application of multiple small isocenters was done. Introduction of the new treatment strategy did not affect the 1-year tumor control rate, which was consistently >90%. However, it did result in a statistically significant reduction of severe posttreatment peritumoral brain edema (from 15.5% to 6.3%; $P < 0.0001$). In **conclusion**, recent technical and methodological achievements of GKS seemingly do not affect its high efficacy in cases of brain metastasis with regard to tumor control. However, it may result in a prominent reduction of treatment-associated morbidity, which is particularly important in patients with large and/or critically located neoplasm.

[335] A case-matched study of stereotactic radiosurgery for patients with multiple brain metastases: comparing treatment results for 1-4 vs \geq 5 tumors: clinical article.

Journal of neurosurgery. 2013;118(6):1258-68

Yamamoto M, Kawabe T, Sato Y, Higuchi Y, Nariai T, Barford BE, Kasuya H, Urakawa Y

PMID: 23600938 DOI: 10.3171/2013.3.JNS121900

OBJECT: Although stereotactic radiosurgery (SRS) alone for patients with 4-5 or more tumors is not a standard treatment, a trend for patients with 5 or more tumors to undergo SRS alone is already apparent. The authors' aim in the present study was to reappraise whether SRS results for \geq 5 tumors differ from those for 1-4 tumors. **METHODS:** This institutional review board-approved retrospective cohort study used the authors' database of prospectively accumulated data that included 2553 consecutive patients who underwent SRS, not in combination with concurrent whole-brain radiotherapy, for brain metastases (METs) between 1998 and 2011. These 2553 patients were divided into 2 groups: 1553 with tumor numbers of 1-4 (Group A) and 1000 with \geq 5 tumors (Group B). Because there was considerable bias in pre-SRS clinical factors between Groups A and B, a case-matched study was conducted. Ultimately, 1096 patients (548 each in Groups A and B) were selected. The standard Kaplan-Meier method was used to determine post-SRS survival and the post-SRS neurological death-free survival times. Competing risk analysis was applied to estimate cumulative incidences of local recurrence, repeat SRS for new lesions, neurological deterioration, and SRS-induced complications. **RESULTS:** The post-SRS median survival time was significantly longer in the 548 Group A patients (7.9 months, 95% CI 7.0-8.9 months) than in the 548 Group B patients (7.0 months 95% [CI 6.2-7.8 months], HR 1.176 [95% CI 1.039-1.331], $p = 0.01$). However, incidences of neurological death were very similar: 10.6% in Group A and 8.2% in Group B ($p = 0.21$). There was no significant difference between the groups in neurological death-free survival intervals (HR 0.945, 95% CI 0.636-1.394, $p = 0.77$). Furthermore, competing risk analyses showed that there were no significant differences between the groups in cumulative incidences of local recurrence (HR 0.577, 95% CI 0.312-1.069, $p = 0.08$), repeat SRS (HR 1.133, 95% CI 0.910-1.409, $p = 0.26$), neurological deterioration (HR 1.868, 95% CI 0.608-1.240, $p = 0.44$), and major SRS-related complications (HR 1.105, 95% CI 0.490-2.496, $p = 0.81$). In the authors' cohort, age \leq 65 years,

female sex, a Karnofsky Performance Scale score \geq 80%, cumulative tumor volume \leq 10 cm³, controlled primary cancer, no extracerebral METs, and neurologically asymptomatic status were significant factors favoring longer survival equally in both groups. **CONCLUSIONS:** This retrospective study suggests that increased tumor number is an unfavorable factor for longer survival. However, the post-SRS median survival time difference, 0.9 months, between the two groups is not clinically meaningful. Furthermore, patients with 5 or more METs have noninferior results compared to patients with 1-4 tumors, in terms of neurological death, local recurrence, repeat SRS, maintenance of good neurological state, and SRS-related complications. A randomized controlled trial should be conducted to test this hypothesis.

[336] Gamma Knife surgery for the treatment of 5 to 15 metastases to the brain: clinical article.

Journal of neurosurgery. 2013;118(6):1250-7

Salvetti DJ, Nagaraja TG, McNeill IT, Xu Z, Sheehan J

PMID: 23540265 DOI: 10.3171/2013.2.JNS121213

OBJECT: It has been generally accepted that Gamma Knife surgery (GKS) is an effective primary or adjunct treatment for patients with 1-4 metastases to the brain. The number of studies detailing the use of GKS for 5 or more brain metastases, however, remains minimal. The aim of the current retrospective study was to elucidate the utility of GKS in patients with 5-15 brain metastases. **METHODS:** Patients were chosen for GKS based on prior MRI of these metastatic lesions and a known primary cancer diagnosis. Magnetic resonance imaging was used post-GKS to assess tumor control; patients were also followed up clinically. Overall survival (OS) from the date of GKS was used as the primary end point. Statistical analysis was performed to identify prognostic factors related to OS. **RESULTS:** Between 2003 and 2012, 96 patients were treated for a total of 704 metastatic brain lesions. The histology of these lesions varied among non-small cell lung cancer (NSCLC), breast cancer, melanoma, renal cancer, and other more rare carcinomas. At the initial treatment, 18 of the patients (18.8%) were categorized in Recursive Partitioning Analysis (RPA) Class 1 and 77 (80.2%) in RPA Class 2; none were in RPA Class 3. The median number of treated lesions was 7 (mean 7.13), and the median planned treatment volume was 6.12 cm³ (range 0.42-57.83 cm³) per patient. The median clinical follow-up was 4.1 months (range 0.1-40.70 months). Actuarial tumor control was calculated to be 92.4% at 6 months, 84.8% at 12 months, and 74.9% at 24 months post-GKS. The median OS was found to be 4.73 months (range 0.4-41.8 months). Multivariate analysis demonstrated that RPA class was a significant predictor of death (HR = 2.263, $p = 0.038$). Number of lesions, tumor histology, Graded Prognostic Assessment score, prior whole-brain radiation therapy, prior resection, prior chemotherapy, patient age, patient sex, controlled primary tumor, extracranial metastases, and planned treatment volume were not significant predictors of OS. **CONCLUSIONS:** In patients with 5-15 brain metastases at presentation, the number of lesions did not predict survival after GKS; however, the RPA class was predictive of OS in this group of patients. Gamma Knife surgery for such patients offers an excellent rate of local tumor control.

[337] Survival following gamma knife radiosurgery for brain metastasis from breast cancer.

Radiation oncology (London, England). 2013;8:131

Jaboin JJ, Ferraro DJ, DeWees TA, Rich KM, Chicoine MR, Dowling JL, Mansur DB, Drzymala RE, Simpson JR, Magnuson WJ, Patel AH, Zoberi I

PMID: 23718256 DOI: 10.1186/1748-717X-8-131

BACKGROUND: Breast cancer is the second most common cause of brain metastases in the United States. Although breast cancer induced brain metastases represent an incurable condition, some patients experience prolonged survival. In this retrospective study, we examine a cohort of patients with brain metastases from breast cancer treated with Gamma Knife stereotactic radiosurgery to identify factors that predict better outcomes. **METHODS:** A retrospective database of 100 patients treated for brain metastases due to breast cancer via Gamma Knife

radiosurgery (GKS) from July 1998 through March 2009 was reviewed. Patients who received radiosurgery as sole treatment, as a planned boost after whole brain radiotherapy or surgical resection, or as salvage after prior whole brain radiation therapy (WBRT) or surgical resection were included. Prognostic factors identified to be significant for survival in previous brain metastasis studies were analyzed for significance by univariate and multivariate Cox analysis. **RESULTS:** Overall, the median brain progression-free survival time was 7.1 months and the median survival time was 12.3 months. No prognostic variables were significant for brain progression-free survival. For patients treated with a planned GKS after WBRT, GKS as sole treatment, GKS salvage after WBRT, GKS boost after surgery, or GKS for surgical salvage the median survival times (MSTs) were as follows: 12.2 months, 12.4 months, 9.5 months, 27.6 months and 33.4 months respectively. Differences between the groups were not significant ($p = 0.06$); however, GKS boost after surgery and GKS for salvage after surgery did have a trend toward better overall survival. **CONCLUSION:** Stereotactic radiosurgery offers good local control and prolonged survival in selected patients. Age and number of lesions are strong predictors of overall survival.

[338] The effect of tumor subtype on the time from primary diagnosis to development of brain metastases and survival in patients with breast cancer.

Journal of neuro-oncology. 2013;112(3):467-72

Sperduto PW, Kased N, Roberge D, Chao ST, Shanley R, Luo X, Sneed PK, Suh J, Weil RJ, Jensen AW, Brown PD, Shih HA, Kirkpatrick J, Gaspar LE, Fiveash JB, Chiang V, Knisely JP, Sperduto CM, Lin N, Mehta M
PMID: 23462853 DOI: 10.1007/s11060-013-1083-9

Our group has previously published the Diagnosis-Specific Graded Prognostic Assessment (GPA) showing the prognostic factors associated with survival in patients with brain metastases (BM). The purpose of this study is to investigate the relationship of breast cancer subtype to the time interval from primary diagnosis (PD) to development of BM (TPDBM), number of BM at initial BM presentation and survival. We analyzed our previously described multi-institutional retrospective database of 865 breast cancer patients treated for newly-diagnosed BM from 1993 to 2010. Several factors found to be associated with survival were incorporated into the Breast-GPA, including tumor subtype. The GPA database was further analyzed to determine if the subtype correlated with the TPDBM, number of BM, and survival from PD. After exclusions for incomplete data, 383 patients remained eligible for analysis. The subtypes were approximated as follows: Luminal B: triple positive; HER2: HER2 positive/ER/PR negative; Luminal A; ER/PR positive/HER2 negative; Basal: triple negative. Patients with Basal (90), HER2 (119), Luminal B (98) and Luminal A (76) tumor subtypes had a median TPDBM of 27.5, 35.8, 47.4 and 54.4 months ($p < 0.01$), median survival from PD of 39.6, 66.4, 90.3 and 72.7 months ($p < 0.01$) and median survival from BM of 7.3, 17.9, 22.9 and 10.0 months ($p < 0.01$), respectively. Tumor subtype is an important prognostic factor for survival in patients with breast cancer and BM. Although TPDBM is not an independent prognostic factor for survival (and thus not part of the Breast-GPA), the TPDBM does correlate with tumor subtype but does not correlate with the number of BM. Patients with Basal and HER2 tumor subtypes have short TPDBM. Prospective studies are needed to determine if screening brain MRIs are indicated in patients with Basal or HER2 subtypes.

[339] Treatment of brainstem metastases with gamma-knife radiosurgery.

Journal of neuro-oncology. 2013;113(1):33-8

Sengoz M, Kabalay IA, Tezcanli E, Peker S, Pamir N
PMID: 23443514 DOI: 10.1007/s11060-013-1086-6

The aim was to investigate the efficacy and safety of gamma-knife stereotactic radiosurgery (SRS) for treating brainstem metastases. The cases of 44 patients who underwent SRS as treatment for 46 brainstem metastases were retrospectively evaluated. The median age was 57 years (range 42-82 years) and the median Karnofsky performance score (KPS) was 80 (range 60-90). The primary tumor was lung carcinoma in 28 cases, breast carcinoma in 7 cases, colon carcinoma in 3 cases, renal cell carcinoma in 3 cases, malignant melanoma in 1 case, and

unknown origin in 2 cases. Of the 46 metastases, 30 were in the pons, 14 were in the mesencephalon, and 2 were in the medulla oblongata. The median volume of the 46 metastases was 0.6 cc (range 0.34-7.3 cc). The median marginal dose of radiation was 16 Gy (range 10-20 Gy). Twenty-three patients (52 %) received whole brain radiotherapy prior to SRS, and 6 (14 %) received this therapy after SRS. In the remaining 15 cases (34 %), SRS was applied as the only treatment. Recursive partitioning analysis, graded prognostic assessment, and basic score for brain metastases were used to predict survival time. Local control was achieved for all but two of the 46 metastases (96 %). The overall survival time after SRS was 8 months. Female gender, KPS >70, mesencephalon tumor location, and response to treatment were associated with longer survival. Basic score for brain metastases class I and recursive partitioning analysis classification were associated with better prognosis. Peri-tumoral changes were detected radiologically at 2 (4 %) of the metastatic lesion sites but neither of these patients exhibited symptoms. Gamma-knife radiosurgery is effective for treating brainstem metastases without a higher risk for radiation necrosis.

[340] Evaluation of mini-mental status examination score after gamma knife radiosurgery as the first radiation treatment for brain metastases.

Journal of neuro-oncology. 2013;112(3):421-5

Nakazaki K, Kano H

PMID: 23408185 DOI: 10.1007/s11060-013-1071-0

This study evaluated the mini-mental status examination (MMSE) scores of patients with brain metastases after gamma knife radiosurgery (GKS) without whole-brain radiation therapy (WBRT). Between January 2009 and June 2011, 119 consecutive patients with new brain metastases were treated with a single session of GKS without WBRT. MMSE scores were determined for all patients before GKS and for surviving patients every 3 months after GKS. We evaluated 76 patients (63.9 %) after GKS. The median pre-GKS MMSE score was 28 (range 3-30). The median age, number of brain metastases, and total volume of brain metastases were 65.5 years (range 40-92 years), 2 (range 1-18), and 4.17 ml (range 0.04-27.0 ml), respectively. The median marginal dose was 22.0 Gy (range 14-24 Gy). Thirty-nine patients (51.3 %) developed new distant lesions. The median MMSE follow-up time was 5.8 months (range 0.9-21.6 months). In 16 of 37 patients (43.2 %) with pre-GKS MMSE scores ≤ 27 , the MMSE scores improved by ≥ 3 points, whereas 15 of all patients (19.7 %) experienced deteriorations of ≥ 3 points. The incidences of 3-point drops due to new distant lesions and adverse radiation effects were 2.6 and 1.3 %, respectively. The 12-month rate of 3-point drops of the MMSE score due to these 2 causes was 4.2 % (1 of 24 patients). A larger tumor volume was a better prognostic factor for an improvement. GKS has a mild effect on neurocognitive function. Mental deterioration of patients with large symptomatic metastatic tumors tended to improve after GKS.

[341] Impacts of HER2-overexpression and molecular targeting therapy on the efficacy of stereotactic radiosurgery for brain metastases from breast cancer.

Journal of neuro-oncology. 2013;112(2):199-207

Yomo S, Hayashi M, Cho N

PMID: 23296546 DOI: 10.1007/s11060-013-1046-1

Advances in chemotherapy for breast cancer (BC) have prolonged overall survival, especially for patients with human epidermal growth factor receptor-2 (HER2) positive cancer. We evaluated the effectiveness and limitations of stereotactic radiosurgery (SRS) for brain metastases (BM) from BC in conjunction with molecular targeting chemotherapy. Outcomes were retrospectively reviewed in 80 consecutive patients who underwent gamma knife SRS for BM from BC between January 2009 and February 2012. The overall survival (OS), neurological death-free survival (NS) and local tumor control endpoints were calculated, and prognostic factors were investigated using proportional hazards models. In 40 patients with HER2-overexpression, treatment results were compared between two sub-groups: lapatinib-based therapy (24 patients) versus non-lapatinib-based therapy (16 patients). The rates of 1- and 2-year OS after SRS were 50 and 26 %, respectively. The median survival time (MST) was 11.4 months. HER2-overexpression ($P <$

0.001), recursive partitioning analysis class (P = 0.018) and total planning target volume on initial SRS (P = 0.004) were associated with OS. The MSTs in HER2-positive and -negative patients were 16.6 and 7.1 months, respectively (P = 0.001). The rates of 1- and 2-year NS were 90 and 78 %, respectively. The rates of 1- and 2-year local tumor control were 84 and 70 %, respectively. Factors associated with local tumor control included lesion volume (P < 0.001) and peripheral dose (P = 0.003). In sub-analysis of patients with HER2-overexpression, lapatinib-based chemotherapy was also associated with better local tumor control (P = 0.002). The 1-year local tumor control rate of the lapatinib group was significantly better than that of the non-lapatinib group (86 vs. 69 %, P < 0.001). SRS is a safe and effective management option for selected patients with BM from BC. Patients with HER2-overexpressing tumors were found to be a distinct subgroup for which a longer survival time can be expected. Synergistic anti-tumor effects of lapatinib on BM in conjunction with SRS were suggested.

[342] Gamma knife surgery of colorectal brain metastases: a high prescription dose of 25 Gy may improve growth control.

World neurosurgery. 2013;79(3-4):525-36

Skeie BS, Enger PO, Ganz JC, Skeie GO, Parr E, Hatteland S, Ystevik B, Heggdal JI, Pedersen PH

PMID: 22120263 DOI: 10.1016/j.wneu.2011.09.019

OBJECTIVE: There are few reports on the effect of gamma knife surgery (GKS) for brain metastases from colorectal cancer. The purpose of this study was to identify prognostic factors for local control, complications, and survival in our series of patients treated with GKS. **METHODS:** Eighty patients (36 males, 44 females) with 140 metastases who received GKS between 1996 and 2008 were retrospectively reviewed. The mean tumor volume was 6.13 (0.01-35.5) cm(3); the prescription dose was 21.1 (10-25.1) Gy and the maximum dose 42.7 (17.2-66.7) Gy; and the tumor cover was 95.0% (72%-100%). **RESULTS:** Growth control was achieved in 93 of 121 tumors (76.9%) and 42 of 68 (61.8%) patients, while treatment failure was seen in 28 of 121 tumors (23.1%). Local control was better if a high prescription dose of 25 Gy was used, 88.4% vs. 71.4% (P = 0.017), or if tumor volume was <5 cm(3) (86.4%), compared with 69.9% for 5-20 cm(3) and 51.9% for >20 cm(3) (P = 0.002). The hazard ratio for local failure with lower prescription doses was 2.8 (P = 0.026) in the unadjusted, and 8.5 (P = 0.055) in the adjusted multivariate analysis (tumor volumes >5 cm(3)). The median survival was 6 months (range 0-75) after GKS. Age <70 years (P < 0.001) and high RPA class (P = 0.032) were associated with longer survival. Fifteen patients (22.1%) had persistent edema on follow-up MRI, possibly because of radiation damage to the tumor. Radiation-induced edema was asymptomatic in 93.8%. We found neither a decrease in the incidence of new metastases nor improved survival when whole-brain radiation therapy was given prior to GKS. **CONCLUSIONS:** GKS provides reasonable local tumor control. Local control rate is highest if the margin dose is 25 Gy and the tumor volume <5 cm(3). Radiation edema was common but rarely symptomatic. Survival is longest for young, well-functioning patients.

[343] Gamma knife radiosurgery for the treatment of cystic cerebral metastases.

International journal of radiation oncology, biology, physics. 2013;85(3):667-71

Ebinu JO, Lwu S, Monsalves E, Arayee M, Chung C, Laperriere NJ, Kulkarni AV, Goetz P, Zadeh G

PMID: 22885145 DOI: 10.1016/j.ijrobp.2012.06.043

PURPOSE: To assess the role of Gamma Knife radiosurgery (GKRS) in the treatment of nonsurgical cystic brain metastasis, and to determine predictors of response to GKRS. **METHODS:** We reviewed a prospectively maintained database of brain metastases patients treated at our institution between 2006 and 2010. All lesions with a cystic component were identified, and volumetric analysis was done to measure percentage of cystic volume on day of treatment and consecutive follow-up MRI scans. Clinical, radiologic, and dosimetry parameters were reviewed to establish the overall response of cystic metastases to GKRS as well as identify potential predictive factors of response. **RESULTS:** A total of 111 lesions in 73 patients were analyzed; 57% of lesions received prior whole-brain radiation

therapy (WBRT). Lung carcinoma was the primary cancer in 51% of patients, 10% breast, 10% colorectal, 4% melanoma, and 26% other. Fifty-seven percent of the patients were recursive partitioning analysis class 1, the remainder class 2. Mean target volume was 3.3 mL (range, 0.1-23 mL). Median prescription dose was 21 Gy (range, 15-24 Gy). Local control rates were 91%, 63%, and 37% at 6, 12, and 18 months, respectively. Local control was improved in lung primary and worse in patients with prior WBRT (univariate). Only lung primary predicted local control in multivariate analysis, whereas age and tumor volume did not. Lesions with a large cystic component did not show a poorer response compared with those with a small cystic component. **CONCLUSIONS:** This study supports the use of GKRS in the management of nonsurgical cystic metastases, despite a traditionally perceived poorer response. Our local control rates are comparable to a matched cohort of noncystic brain metastases, and therefore the presence of a large cystic component should not deter the use of GKRS. Predictors of response included tumor subtype. Prior WBRT decreased effectiveness of SRS for local control rates.

[344] Survival of brain metastatic patients treated with gamma knife radiosurgery alone.

Clinical neurology and neurosurgery. 2013;115(3):260-5

Chiou SM

PMID: 22705456 DOI: 10.1016/j.clineuro.2012.05.018

PURPOSE: To evaluate the impact of gamma knife radiosurgery (GKRS) alone on the survival of brain metastasis patients. **METHODS:** Fifty patients, 17 men and 33 women, with 169 metastatic tumors were retrospectively reviewed. Before therapy, their mean Karnofsky Performance Score was 78. The majority of their primary cancers stemmed from the lung (56%). Thirty-five patients harbored multiple tumors. The mean tumor volume was 3.7 ml. The mean margin dose was 16 Gy. The mean/median clinical follow-up period was 37/25 weeks. **RESULTS:** The overall image-proven tumor control rate was 76%, and the median tumor progression-free period was 26 weeks after radiosurgery. The survival rate of the patients was 58% and 30% at 6 and 12 months, respectively, and the overall median post-radiosurgery survival time was 38 weeks. Both uni- and multi-variate Cox analyses demonstrated that patients with KPS >=80 or who were in Recursive Partitioning Analysis Class I survived significantly longer (p<0.05). **CONCLUSIONS:** Patients treated with GKRS alone can prolong their median lifespan by a range of 6-10 months if they are in a good pre-GKRS functional state.

[345] Cavity volume dynamics after resection of brain metastases and timing of postresection cavity stereotactic radiosurgery.

Neurosurgery. 2013;72(2):180-5; discussion 185

Atalar B, Choi CY, Harsh GR 4th, Chang SD, Gibbs IC, Adler JR, Soltys SG

PMID: 23149969 DOI: 10.1227/NEU.0b013e31827b99f3

BACKGROUND: An alternative treatment option to whole-brain irradiation after surgical resection of brain metastases is resection cavity stereotactic radiosurgery (SRS). **OBJECTIVE:** To review the dynamics of cavity volume change after surgical resection with the goal of determining the optimal timing for cavity SRS. **METHODS:** Preresection tumor, postresection/pre-SRS cavity, and post-SRS cavity volumes were measured for 68 cavities in 63 patients treated with surgery and postresection cavity SRS. Percent differences between volumes were calculated and correlation analyses were performed to assess volume changes before and after SRS. **RESULTS:** For the majority of tumors, the postresection cavity volume was smaller than the preresection tumor volume by a median percent volume change of -29% (range, -82% to 1258%), with larger preresection tumors resulting in greater cavity shrinkage (P < .001). To determine the optimal timing for cavity SRS, we examined cavity volume dynamics by comparing the early postresection (postoperative days 0-3) and treatment planning magnetic resonance imaging scans (median time to magnetic resonance imaging, 20 days; range, 9-33 days) and found no association between the postresection day number and volume change (P = .75). The volume decrease resulting from tumor resection was offset by the addition of a 2-mm clinical target volume margin, which is our current technique. **CONCLUSION:** The greatest volume change occurs immediately after

surgery (postoperative days 0-3) with no statistically significant volume change occurring up to 33 days after surgery for most patients. Therefore, there is no benefit of cavity shrinkage in waiting longer than the first 1 to 2 weeks to perform cavity SRS.

[346] Stereotactic radiosurgery for the treatment of melanoma and renal cell carcinoma brain metastases.

Oncology reports. 2013;29(2):407-12

Lwu S, Goetz P, Monsalves E, Aryaee M, Ebinu J, Laperriere N, Menard C, Chung C, Millar BA, Kulkarni AV, Bernstein M, Zadeh G
PMID: 23151681 DOI: 10.3892/or.2012.2139

Renal cell carcinoma (RCC) and melanoma brain metastases have traditionally been considered radioresistant lesions when treated with conventional radiotherapeutic modalities. Radiosurgery provides high-dose radiation to a defined target volume with steep fall off in dose at lesion margins. Recent evidence suggests that stereotactic radiosurgery (SRS) is effective in improving local control and overall survival for a number of tumor subtypes including RCC and melanoma brain metastases. The purpose of this study was to compare the response rate to SRS between RCC and melanoma patients and to identify predictors of response to SRS for these 2 specific subtypes of brain metastases. We retrospectively reviewed a prospectively maintained database of all brain metastases treated with Gamma Knife SRS at the University Health Network (Toronto, Ontario) between October 2007 and June 2010, studying RCC and melanoma patients. Demographics, treatment history and dosimetry data were collected; and MRIs were reviewed for treatment response. Log rank, Cox proportional hazard ratio and Kaplan-Meier survival analysis using SPSS were performed. A total of 103 brain metastases patients (41 RCC; 62 melanoma) were included in the study. The median age, Karnofsky performance status score and Eastern Cooperative Oncology Group performance score was 52 years (range 27-81), 90 (range 70-100) and 1 (range 0-2), respectively. Thirty-four lesions received adjuvant chemotherapy and 56 received pre-SRS whole brain radiation therapy. The median follow-up, prescription dose, Radiation Therapy Oncology Group conformity index, target volume and number of shots was 6 months (range 1-41 months), 21 Gy (range 15-25 Gy), 1.93 (range 1.04-9.76), 0.4 cm³ (range 0.005-13.36 cm³) and 2 (range 1-22), respectively. Smaller tumor volume (P=0.007) and RCC pathology (P=0.04) were found to be positive predictors of response. Actuarial local control rate for RCC and melanoma combined was 89% at 6 months, 84% at 12 months, 76% at 18 months and 61% at 24 months. Local control at 12 months was 91 and 75% for RCC and melanoma, respectively. SRS is a valuable treatment option for local control of RCC and melanoma brain metastases. Smaller tumor volume and RCC pathology, predictors of response, suggest distinct differences in tumor biology and the extent of radioresponse between RCC and melanoma.

[347] Validity of two recently-proposed prognostic grading indices for lung, gastro-intestinal, breast and renal cell cancer patients with radiosurgically-treated brain metastases.

Journal of neuro-oncology. 2013;111(3):327-35

Yamamoto M, Serizawa T, Sato Y, Kawabe T, Higuchi Y, Nagano O, Barfod BE, Ono J, Kasuya H, Urakawa Y

PMID: 23224746 DOI: 10.1007/s11060-012-1019-9

We tested the validity of two prognostic indices for stereotactic radiosurgically (SRS)-treated patients with brain metastases (BMs) from five major original cancer categories. The two indices are Diagnosis-Specific Graded Prognostic Assessment (DS-GPA) and our Modified Recursive Partitioning Analysis (RPA). Forty-six hundred and eight BM patients underwent gamma knife SRS during the 1998-2011 period. Primary cancer categories were non-small cell lung cancer (NSCLC, 2827 patients), small cell lung cancer (SCLC, 460), gastro-intestinal cancer (GIC, 582), breast cancer (BC, 547) and renal cell cancer (RCC, 192). There were statistically significant survival differences among patients stratified into four groups based on the DS-GPA systems (p < 0.001) in all five original cancer categories. In the NSCLC category, there were statistically significant mean survival time (MST) differences (p

< 0.001) among the four groups without overlapping of 95 % confidence intervals (CIs) between any two pairs of groups with the DS-GPA system. However, among the SCLC, GIC, BC and RCC categories, MST differences between some pairs of groups failed to reach statistical significance with this system. There were, however, statistically significant MST differences (p < 0.001) among the three groups without overlapping of 95 % CIs between any two pairs of groups with the Modified RPA system in all five categories. The DS-GPA system is applicable to our set of patients with NSCLC only. However, the Modified RPA system was shown to be applicable to patients with five primary cancer categories. This index should be considered when designing future clinical trials involving BM patients.

[348] Leukoencephalopathy after whole-brain radiation therapy plus radiosurgery versus radiosurgery alone for metastatic lung cancer.

Cancer. 2013;119(1):226-32

Monaco EA 3rd, Faraji AH, Berkowitz O, Parry PV, Hadelsberg U, Kano H, Niranjana A, Kondziolka D, Lunsford LD

PMID: 22707281 DOI: 10.1002/cncr.27504

BACKGROUND: As systemic therapies improve and patients live longer, concerns mount about the toxicity of whole-brain radiation therapy (WBRT) for treatment of brain metastases. Development of delayed white matter abnormalities indicative of leukoencephalopathy have been correlated with cognitive dysfunction. This study assesses the risk of imaging-defined leukoencephalopathy in patients whose management included WBRT in addition to stereotactic radiosurgery (SRS). This risk is compared to patients who only underwent SRS. **METHODS:** We retrospectively compared 37 patients with non-small cell lung cancer who underwent WBRT plus SRS to 31 patients who underwent only SRS. All patients survived at least 1 year after treatment. We graded the development of delayed white matter changes on magnetic resonance imaging using a scale to evaluate T2/FLAIR (fluid attenuated image recovery) images: grade 1 = little or no white matter hyperintensity; grade 2 = limited periventricular hyperintensity; and grade 3 = diffuse white matter hyperintensity. **RESULTS:** Patients treated with WBRT and SRS had a significantly greater incidence of delayed white matter leukoencephalopathy compared to patients who underwent SRS alone (P < .001). On final imaging, 36 of 37 patients (97.3%) treated by WBRT developed leukoencephalopathy (25% with grade 2; 70.8% with grade 3). Only 1 patient treated with SRS alone developed leukoencephalopathy. **CONCLUSIONS:** Risk of leukoencephalopathy in patients treated with SRS alone for brain metastases was significantly lower than that for patients treated with WBRT plus SRS. A prospective study is necessary to correlate these findings with neurocognition and quality of life. These data supplement existing reports regarding the differential effects of WBRT and SRS on normal brain structure and function.

[349] Gamma knife radiosurgery for skull base malignancies.

Clinical neurology and neurosurgery. 2013;115(1):44-8

Pan J, Liu AL, Wang ZC

PMID: 22579646 DOI: 10.1016/j.clineuro.2012.04.013

BACKGROUND: Skull base malignancies are problematic. We evaluated the efficacy and toxicity of gamma knife radiosurgery (GKRS) in the treatment of patients with primary and secondary malignancies in the skull base. **METHODS:** The data of 43 patients were retrospectively analyzed. Sixteen of these patients had a primary skull base malignancy, and 27 patients had skull base metastasis or an invasion from other cancers. The median tumor volume was 7.2 cm³ (range, 0.6-33.4). The median prescription margin dose was 14.0 Gy (range, 10-16). Nine patients with tumor regrowth after initial reduction received another treatment. **RESULTS:** The median follow-up time was 14 months (range, 1-60). Following GKRS, the progression-free survival was 89% and 62% at 1 and 2 years, respectively, and the overall survival rate was 74% and 45% at 1 and 2 years, respectively. Nineteen (44%) patients reported an improvement following GKRS. One patient (2%) reported decreased vision, which was considered to be a side effect from cumulative GKRS doses. **CONCLUSION:** Gamma knife radiosurgery is an effective treatment for primary and secondary malignant tumors in the skull

base as initial monotherapy or as an adjunct therapy to surgery or radiotherapy.

[350] Efficacy and limitations of salvage gamma knife radiosurgery for brain metastases of small-cell lung cancer after whole-brain radiotherapy.

Acta neurochirurgica. 2013;155(1):107-13; discussion 113-4

Nakazaki K, Higuchi Y, Nagano O, Serizawa T

PMID: 23065044 DOI: 10.1007/s00701-012-1520-0

BACKGROUND: The efficacy and limitations of salvage gamma knife surgery (GKS) have not been thoroughly described. This study evaluated the efficacy of GKS for treating brain metastases associated with small-cell lung cancer (SCLC) after whole-brain radiotherapy (WBRT) as the first-line radiation therapy.

METHODS: Forty-four patients with recurrent or new SCLC-associated brain metastases underwent GKS after receiving WBRT (median age, 62 years; median duration between WBRT and first GKS, 8.8 months). The median Karnofsky performance status (KPS) score was 100 (range, 40-100), and the median number of brain metastases at the first GKS was five. Ten patients who partially or completely responded to chemotherapy received prophylactic cranial irradiation (PCI) for limited disease. **RESULTS:** The median prescribed dose and number of lesions treated with the initial GKS were 20.0 Gy and 3.5, respectively, and the tumor control rate was 95.8% (median follow-up period, 4.0 months). The 6-month new lesion-free survival, functional preservation rates, and overall survival were 50.0%, 94.7%, and 5.8 months, respectively. Neurological death occurred in 17.9% of cases. The poor prognostic factors for new lesion-free survival time and functional preservation were >5 brain metastases and carcinomatous meningitis, respectively. Poor prognostic factors for survival time were KPS <70, >10 brain metastases, diameter of the largest tumor >20 mm, and carcinomatous meningitis. Median overall survival time from brain metastasis diagnosis was 16.9 months. **CONCLUSIONS:** GKS may be an effective option for controlling SCLC-associated brain metastases after WBRT and for preventing neurological death in patients without carcinomatous meningitis.

[351] Delayed complications in patients surviving at least 3 years after stereotactic radiosurgery for brain metastases.

International journal of radiation oncology, biology, physics. 2013;85(1):53-60

Yamamoto M, Kawabe T, Higuchi Y, Sato Y, Nariai T, Barford BE, Kasuya H, Urakawa Y

PMID: 22652110 DOI: 10.1016/j.ijrobp.2012.04.018

PURPOSE: Little is known about delayed complications after stereotactic radiosurgery in long-surviving patients with brain metastases. We studied the actual incidence and predictors of delayed complications. **PATIENTS AND**

METHODS: This was an institutional review board-approved, retrospective cohort study that used our database. Among our consecutive series of 2000 patients with brain metastases who underwent Gamma Knife radiosurgery (GKRS) from 1991-2008, 167 patients (8.4%, 89 women, 78 men, mean age 62 years [range, 19-88 years]) who survived at least 3 years after GKRS were studied. **RESULTS:** Among the 167 patients, 17 (10.2%, 18 lesions) experienced delayed complications (mass lesions with or without cyst in 8, cyst alone in 8, edema in 2) occurring 24.0-121.0 months (median, 57.5 months) after GKRS. The actuarial incidences of delayed complications estimated by competing risk analysis were 4.2% and 21.2% at the 60th month and 120th month, respectively, after GKRS. Among various pre-GKRS clinical factors, univariate analysis demonstrated tumor volume-related factors: largest tumor volume (hazard ratio [HR], 1.091; 95% confidence interval [CI], 1.018-1.154; $P=.0174$) and tumor volume ≤ 10 cc vs >10 cc (HR, 4.343; 95% CI, 1.444-12.14; $P=.0108$) to be the only significant predictors of delayed complications. Univariate analysis revealed no correlations between delayed complications and radiosurgical parameters (ie, radiosurgical doses, conformity and gradient indexes, and brain volumes receiving >5 Gy and >12 Gy). After GKRS, an area of prolonged enhancement at the irradiated lesion was shown to be a possible risk factor for the development of delayed complications (HR, 8.751; 95% CI, 1.785-157.9; $P=.0037$). Neurosurgical interventions were performed in 13 patients (14 lesions) and mass removal for 6 lesions and Ommaya reservoir placement for

the other 8. The results were favorable. **CONCLUSIONS:** Long-term follow-up is crucial for patients with brain metastases treated with GKRS because the risk of complications long after treatment is not insignificant. However, even when delayed complications occur, favorable outcomes can be expected with timely neurosurgical intervention.

2012

[352] Gamma Knife surgery for patients with brainstem metastases.

Journal of neurosurgery. 2012;117 Suppl:23-30

Kawabe T, Yamamoto M, Sato Y, Barford BE, Urakawa Y, Kasuya H, Mineura K

PMID: 23205785 DOI: 10.3171/2012.7.GKS12977

OBJECT: Because brainstem metastases are not deemed resectable, stereotactic radiosurgery (SRS) is the only treatment modality expected to achieve a radical cure. The authors describe their treatment results, focusing particularly on how long patients can survive without neurological deterioration following SRS for brainstem metastases. **METHODS:** This was an institutional review board-approved, retrospective cohort study in which the authors pulled from their database information on 2553 consecutive patients with brain metastases who underwent Gamma Knife surgery (GKS) at the Mito GammaHouse between July 1998 and July 2011. Among the 2553 patients, excluding cases in which there was meningeal dissemination, 200 cases of brainstem metastases (78 women and 122 men with a mean age of 64 years [range 36-86 years]) were identified and analyzed. The most common primary site was the lung (137 patients) followed by the gastrointestinal tract (24 patients), breast (17 patients), kidney (12 patients), and others (10 patients). Among the 200 patients, 15 patients (7.5%) harbored at least 2 tumors in the brainstem: 11 patients had 2 tumors, 2 patients had 3 tumors, and 1 patient each had 4 or 5 tumors. Therefore, a total of 222 tumors were irradiated. These 222 tumors were located in the pons (121 lesions), the midbrain (65 lesions), and the medulla oblongata (36 lesions). The mean and median tumor volumes were 1.3 and 0.2 cm³ (range 0.005-10.7 cm³), and the median peripheral radiation dose was 18.0 Gy (range 12.0-25.0 Gy). **RESULTS:** The overall median survival time (MST) was 6.0 months. Distribution of MSTs across Recursive Partitioning Analysis (RPA) classes showed that the MSTs were 9.4 months in Class I (20 patients), 6.0 months in Class II (171 patients), and 1.9 months in Class III (9 patients). Better Karnofsky Performance Scale score, single metastasis, and well-controlled primary tumor were significant predictive factors for longer survival. The neurological and qualitative survival rates were 90.8% and 89.2%, respectively, at 24 months post-GKS. Better KPS score and smaller tumor volume tended to be associated with prolonged qualitative survival. Follow-up imaging studies were available for 129 patients (64.5%). The tumor control rate was 81.8% at 24 months post-GKS. Smaller tumor volume tended to contribute to tumor control. **CONCLUSIONS:** The present results indicate that GKS is effective in the treatment of brainstem metastases, particularly from the viewpoint of maintaining a good neurological condition in the patient.

[353] Validation of Recursive Partitioning Analysis and Diagnosis-Specific Graded Prognostic Assessment in patients treated initially with radiosurgery alone.

Journal of neurosurgery. 2012;117 Suppl:38-44

Likhacheva A, Pinnix CC, Parikh N, Allen PK, Guha-Thakurta N, McAleer M,

Sulman EP, Mahajan A, Shiu A, Luo D, Chiu M, Brown PD, Prabhu SS, Chang EL

PMID: 23205787 DOI: 10.3171/2012.3.GKS1289

OBJECT: Brain metastases present a therapeutic challenge because patients with metastatic cancers live longer now than in the recent past due to systemic therapies that, while effective, may not penetrate the blood-brain barrier. In the present study the authors sought to validate the Diagnosis-Specific Graded Prognostic Assessment (DS-GPA), a new prognostic index that takes into account the histological characteristics of the primary tumor, and the Radiation Therapy

Ontology Group Recursive Partitioning Analysis (RPA) system by using a single-institution database of patients who were treated initially with stereotactic radiosurgery (SRS) alone for brain metastases. **METHODS:** Investigators retrospectively identified adult patients who had undergone SRS at a single institution, MD Anderson Cancer Center, for initial treatment of brain metastases between 2003 and 2010 but excluded those who had undergone craniotomy and/or whole-brain radiation therapy at an earlier time; the final number was 251. The Leksell Gamma Knife was used to treat 223 patients, and a linear accelerator was used to treat 28 patients. The patient population was grouped according to DS-GPA scores as follows: 0-0.5 (7 patients), 1 (33 patients), 1.5 (25 patients), 2 (63 patients), 2.5 (14 patients), 3 (68 patients), and 3.5-4 (41 patients). The same patients were also grouped according to RPA classes: 1 (24 patients), 2 (216 patients), and 3 (11 patients). The most common histological diagnoses were non-small cell lung cancer (34%), melanoma (29%), and breast carcinoma (16%). The median number of lesions was 2 (range 1-9) and the median total tumor volume was 0.9 cm³ (range 0.3-22.9 cm³). The median radiation dose was 20 Gy (range 14-24 Gy). Stereotactic radiosurgery was performed as the sole treatment (62% of patients) or combined with a salvage treatment consisting of SRS (22%), whole-brain radiation therapy (12%), or resection (4%). The median duration of follow-up was 9.4 months. **RESULTS:** In this patient group the median overall survival was 11.1 months. The DS-GPA prognostic index divided patients into prognostically significant groups. Median survival times were 2.8 months for DS-GPA Scores 0-0.5, 3.9 months for Score 1, 6.6 months for Score 1.5, 12.9 months for Score 2, 11.9 months for Score 2.5, 12.2 months for Score 3, and 31.4 months for Scores 3.5-4 ($p < 0.0001$). In the RPA groups, the median overall survival times were 38.8 months for Class 1, 9.4 months for Class 2, and 2.8 months for Class 3 ($p < 0.0001$). Neither the RPA class nor the DS-GPA score was prognostic for local tumor control or new lesion-free survival. A multivariate analysis revealed that patient age > 60 years, Karnofsky Performance Scale score $\leq 80\%$, and total lesion volume > 2 cm³ were significant adverse prognostic factors for overall survival. **CONCLUSIONS:** Application of the DS-GPA to a database of patients with brain metastases who were treated with SRS appears to be valid and offers additional prognostic refinement over that provided by the RPA. The DS-GPA may also allow for improved selection of patients to undergo initial SRS alone and should be studied further.

[354] Testing different brain metastasis grading systems in stereotactic radiosurgery: Radiation Therapy Oncology Group's RPA, SIR, BSBM, GPA, and modified RPA.

Journal of neurosurgery. 2012;117 Suppl:31-7
Serizawa T, Higuchi Y, Nagano O, Hirai T, Ono J, Saeki N, Miyakawa A
PMID: 23205786 DOI: 10.3171/2012.8.GKS12710
OBJECT: The authors conducted validity testing of the 5 major reported indices for radiosurgically treated brain metastases- the original Radiation Therapy Oncology Group's Recursive Partitioning Analysis (RPA), the Score Index for Radiosurgery in Brain Metastases (SIR), the Basic Score for Brain Metastases (BSBM), the Graded Prognostic Assessment (GPA), and the subclassification of RPA Class II proposed by Yamamoto-in nearly 2500 cases treated with Gamma Knife surgery (GKS), focusing on the preservation of neurological function as well as the traditional endpoint of overall survival. **METHODS:** The authors analyzed data from 2445 cases treated with GKS by the first author (T.S.), the primary surgeon. The patient group consisted of 1716 patients treated between January 1998 and March 2008 (the Chiba series) and 729 patients treated between April 2008 and December 2011 (the Tokyo series). The interval from the date of GKS until the date of the patient's death (overall survival) and impaired activities of daily living (qualitative survival) were calculated using the Kaplan-Meier method, while the absolute risk for two adjacent classes of each grading system and both hazard ratios and 95% confidence intervals were estimated using the Cox proportional hazards model. **RESULTS:** For overall survival, there were highly statistically significant differences between each two adjacent patient groups characterized by class or score (all p values < 0.001), except for GPA Scores 3.5-

4.0 and 3.0. The SIR showed the best statistical results for predicting preservation of neurological function. Although no other grading systems yielded statistically significant differences in qualitative survival, the BSBM and the modified RPA appeared to be better than the original RPA and GPA. **CONCLUSIONS:** The modified RPA subclassification, proposed by Yamamoto, is well balanced in scoring simplicity with respect to case number distribution and statistical results for overall survival. However, a new or revised grading system is necessary for predicting qualitative survival and for selecting the optimal treatment for patients with brain metastasis treated by GKS.

[355] Role of Gamma Knife surgery in patients with 5 or more brain metastases.

Journal of neurosurgery. 2012;117 Suppl:5-12
Mohammadi AM, Recinos PF, Barnett GH, Weil RJ, Vogelbaum MA, Chao ST, Suh JH, Marko NF, Elson P, Neyman G, Angelov L
PMID: 23205782 DOI: 10.3171/2012.8.GKS12983
OBJECT: The authors evaluated overall survival and factors predicting outcome in patients with ≥ 5 brain metastases who were treated with Gamma Knife surgery (GKS). **METHODS:** Medical records from patients with ≥ 5 brain metastases treated with GKS between 1997 and 2010 at the Cleveland Clinic Gamma Knife Center were retrospectively reviewed. Patient demographics, tumor characteristics, treatment-related factors, and outcome data were evaluated. **RESULTS:** One hundred seventy patients were identified, with a median age of 58 years. The female/male ratio was 1.2:1. Gamma Knife surgery was used as an upfront treatment in 35% of patients and as salvage treatment in 65% of patients with multiple brain metastases. The median overall survival after GKS was 6.7 months (95% CI 5.5-8.1). At the time of GKS, 128 patients (75%) had concurrent extracranial metastases, and in 69 patients (41%) multiple extracranial sites were involved. Ninety-two patients (54%) had a history of whole-brain radiation therapy, and 158 patients (93%) had a Karnofsky Performance Scale (KPS) score ≥ 70 . The median total intracranial disease volume was 3.2 cm³ (range 0.2-37.2 cm³). A total intracranial tumor volume ≥ 10 cm³ was observed in 32 patients (19%). Lower KPS score at the time of treatment ($p < 0.0001$), patient age > 60 years ($p = 0.004$), multiple extracranial metastases ($p = 0.0001$), and greater intracranial burden of disease ($p = 0.03$) were prognostic factors for poor outcome in the univariate and multivariate analyses. **CONCLUSIONS:** In this study, GKS was safe and effective for upfront and salvage treatment in patients with ≥ 5 brain metastases. Gamma Knife surgery should be considered as an additional treatment modality for these patients, especially in the subset of patients with favorable prognostic factors.

[356] Validity of three recently proposed prognostic grading indexes for breast cancer patients with radiosurgically treated brain metastases.

International journal of radiation oncology, biology, physics. 2012;84(5):1110-5
Yamamoto M, Kawabe T, Higuchi Y, Sato Y, Barfod BE, Kasuya H, Urakawa Y
PMID: 22516807 DOI: 10.1016/j.ijrobp.2012.02.040
PURPOSE: We tested the validity of 3 recently proposed prognostic indexes for breast cancer patients with brain metastases (METs) treated radiosurgically. The 3 indexes are Diagnosis-Specific Graded Prognostic Assessment (DS-GPA), New Breast Cancer (NBC)-Recursive Partitioning Analysis (RPA), and our index, subclassification of RPA class II patients into 3 sub-classes (RPA class II-a, II-b and II-c) based on Karnofsky performance status, tumor number, original tumor status, and non-brain METs. **METHODS AND MATERIALS:** This was an institutional review board-approved, retrospective cohort study using our database of 269 consecutive female breast cancer patients (mean age, 55 years; range, 26-86 years) who underwent Gamma Knife radiosurgery (GKRS) alone, without whole-brain radiation therapy, for brain METs during the 15-year period between 1996 and 2011. The Kaplan-Meier method was used to estimate the absolute risk of each event. **RESULTS:** Kaplan-Meier plots of our patient series showed statistically significant survival differences among patients stratified into 3, 4, or 5 groups based on the 3 systems ($P < .001$). However, the mean survival time (MST) differences between some pairs of groups failed to reach statistical significance

with all 3 systems. Thus, we attempted to regrade our 269 breast cancer patients into 3 groups by modifying our aforementioned index along with the original RPA class I and III, (ie, RPA I+II-a, II-b, and II-c+III). There were statistically significant MST differences among these 3 groups without overlap of 95% confidence intervals (CIs) between any 2 pairs of groups: 18.4 (95% CI = 14.0-29.5) months in I+II-a, 9.2 in II-b (95% CI = 6.8-12.9, $P < .001$ vs I+II-a) and 5.0 in II-c+III (95% CI = 4.2-6.8, $P < .001$ vs II-b). **CONCLUSIONS:** As none of the new grading systems, DS-GPS, BC-RPA and our system, was applicable to our set of radiosurgically treated patients for comparing survivals after GKRS, we slightly modified our system for breast cancer patients.

[357] Breast cancer subtype affects patterns of failure of brain metastases after treatment with stereotactic radiosurgery.

Journal of neuro-oncology. 2012;110(3):381-8

Vern-Gross TZ, Lawrence JA, Case LD, McMullen KP, Bourland JD, Metheny-Barlow LJ, Ellis TL, Tatter SB, Shaw EG, Urbanic JJ, Chan MD
PMID: 23001361 DOI: 10.1007/s11060-012-0976-3

We investigate the variance in patterns of failure after Gamma Knife radiosurgery (GKRS) for patients with brain metastases based on the subtype of the primary breast cancer. Between 2000 and 2010, 154 breast cancer patients were treated with GKRS for brain metastases. Tumor subtypes were approximated based on hormone receptor (HR) and HER2 status of the primary cancer: Luminal A/B (HR+/HER2-); HER2 (HER2+/HR-); Luminal HER2 (HR+/HER2+), Basal (HR-/HER2-), and then based on HER2 status alone. The median follow-up period was 54 months. Kaplan-Meier method was used to estimate survival times. Multivariable analysis was performed using Cox regression models. Median number of lesions treated was two (range 1-15) with a median dose of 20 Gy (range 9-24 Gy). Median overall survival (OS) was 7, 9, 11 and 22 months for Basal, Luminal A/B, HER2, and Luminal HER2, respectively ($p = 0.001$), and was 17 and 8 months for HER2+ and HER(-) patients, respectively ($p < 0.001$). Breast cancer subtype did not predict time to local failure ($p = 0.554$), but did predict distant brain failure rate (76, 47, 47, 36 % at 1 year for Basal, Luminal A/B, HER2, and Luminal HER2 respectively, $p < 0.001$). An increased proportion of HER2+ patients experienced neurologic death (46 vs 31 %, $p = 0.066$). Multivariate analysis revealed that HER2+ patients ($p = 0.007$) independently predicted for improved survival. Women with basal subtype have high rates of distant brain failure and worsened survival. Our data suggest that differences in biologic behavior of brain metastasis occur across breast cancer subtypes.

[358] Impact of triple-negative phenotype on prognosis of patients with breast cancer brain metastases.

International journal of radiation oncology, biology, physics. 2012;84(3):612-8

Xu Z, Schlesinger D, Toulmin S, Rich T, Sheehan J
PMID: 22436795 DOI: 10.1016/j.ijrobp.2011.12.054

PURPOSE: To elucidate survival times and identify potential prognostic factors in patients with triple-negative (TN) phenotype who harbored brain metastases arising from breast cancer and who underwent stereotactic radiosurgery (SRS).

METHODS AND MATERIALS: A total of 103 breast cancer patients with brain metastases were treated with SRS and then studied retrospectively. Twenty-four patients (23.3%) were TN. Survival times were estimated using the Kaplan-Meier method, with a log-rank test computing the survival time difference between groups. Univariate and multivariate analyses to predict potential prognostic factors were performed using a Cox proportional hazard regression model.

RESULTS: The presence of TN phenotype was associated with worse survival times, including overall survival after the diagnosis of primary breast cancer (43 months vs. 82 months), neurologic survival after the diagnosis of intracranial metastases, and radiosurgical survival after SRS, with median survival times being 13 months vs. 25 months and 6 months vs. 16 months, respectively ($p < 0.002$ in all three comparisons). On multivariate analysis, radiosurgical survival benefit was associated with non-TN status and lower recursive partitioning analysis class at the initial SRS. **CONCLUSION:** The TN phenotype represents a significant

adverse prognostic factor with respect to overall survival, neurologic survival, and radiosurgical survival in breast cancer patients with intracranial metastasis. Recursive partitioning analysis class also served as an important and independent prognostic factor.

[359] Regression curves of brain metastases after gamma knife irradiation: Difference by tumor and patient characteristics.

Cancer science. 2012;103(11):1967-73

Kosaki K, Shibamoto Y, Hirai T, Hatano M, Tomita N, Kobayashi T, Mori Y
PMID: 22988917 DOI: 10.1111/j.1349-7006.2012.02392.x

Regression curves and local control rates of brain metastases after gamma knife treatment were evaluated to investigate differences in tumor response to radiation. A total of 203 metastases were serially evaluated using contrast-enhanced MRI (or computed tomography) at 1, 2, 3, 4.5 and 6 months after a 20-Gy dose. Differences were evaluated in regression curves and control rates between tumors ≥ 10 mm and tumors < 10 mm in mean diameter, among three major histological subtypes of lung cancer, among adenocarcinomas of the lung, breast and colorectum, and between tumors in patients with above and below median hemoglobin levels. Smaller tumors shrank faster and yielded better control rates than larger tumors. Metastases from small cell and squamous cell carcinomas of the lung shrank faster than those from lung adenocarcinoma, but 6-month control rates were not different. Breast adenocarcinomas tended to shrink faster than lung adenocarcinomas, but the control rates were not different among adenocarcinomas of the lung, breast and colorectum. Tumors in patients with higher hemoglobin levels tended to shrink faster but the control rates were not different. Small cell and squamous cell carcinomas of the lung regress more rapidly than adenocarcinomas, although local control rates might not differ significantly.

[360] Clinical outcomes of brain metastases treated with Gamma Knife radiosurgery with 3.0 T versus 1.5 T MRI-based treatment planning: have we finally optimised detection of occult brain metastases?

Journal of medical imaging and radiation oncology. 2012;56(5):554-60

Loganathan AG, Chan MD, Alphonse N, Peiffer AM, Johnson AJ, McMullen KP, Urbanic JJ, Saconn PA, Bourland JD, Munley MT, Shaw EG, Tatter SB, Ellis TL
PMID: 23043576 DOI: 10.1111/j.1754-9485.2012.02429.x

INTRODUCTION: The goal of this study was to determine if clinically relevant endpoints were changed by improved MRI resolution during radiosurgical treatment planning. **METHODS AND MATERIALS:** Between 2003 and 2008, 200 consecutive patients with brain metastases treated with Gamma Knife radiosurgery (GKRS) using either 1.5 T or 3.0 T MRI for radiosurgical treatment planning were retrospectively analysed. The number of previously undetected metastases at time of radiosurgery, distant brain failures, time delay to whole brain radiotherapy (WBRT), overall survival and likelihood of neurological death were determined. **RESULTS:** Additional metastases were detected in 31.3% and 24.5% of patients at time of radiosurgery with 3.0 T and 1.5 T MRI, respectively ($P = 0.27$). Patients with multiple metastases at diagnostic scan were more likely to have additional metastases detected by 3.0 T MRI ($P < 0.1$). Median time to distant brain failure was 4.87 months and 5.43 months for the 3.0 T and 1.5 T cohorts, respectively ($P = 0.44$). Median time to WBRT was 5.8 months and 5.3 months for the 3.0 T and 1.5 T cohorts, respectively ($P = 0.87$). Median survival was 6.4 months for the 3.0 T cohort, and 6.1 months for the 1.5 T cohort ($P = 0.71$). Likelihood of neurological death was 25.3% and 16.7% for the 3.0 and 1.5 T populations, respectively ($P = 0.26$). **CONCLUSIONS:** The 3.0 T MRI-based treatment planning for GKRS did not appear to affect the likelihood of distant brain failure, the need for WBRT or the likelihood of neurological death in this series.

[361] Multiple gamma knife radiosurgery for multiple metachronous brain metastases associated with lung cancer : survival time.

Journal of Korean Neurosurgical Society. 2012;52(4):334-8

Kim HS, Koh EJ, Choi HY

PMID: 23133721 DOI: 10.3340/jkns.2012.52.4.334

OBJECTIVE: We compared the survival time between patients with multiple gamma knife radiosurgery (GKRS) and patients with a single GKRS plus whole brain radiation therapy (WBRT), in patients with multiple metachronous brain metastases from lung cancer. **METHODS:** From May 2006 to July 2010, we analyzed 31 patients out of 112 patients who showed multiple metachronous brain metastases. 20 out of 31 patients underwent multiple GKRS (group A) and 11 patients underwent a single GKRS plus WBRT (group B). We compared the survival time between group A and B. Kaplan-Meier method and Cox proportional hazards were used to analyze relationship between survival and 1) the number of lesions in each patient, 2) the average volume of lesions in each patient, 3) the number of repeated GKRS, and 4) the interval of development of new lesions, respectively. **RESULTS:** Median survival time was 18 months (range 6-50 months) in group A and 6 months (range 3-18 months) in group B. Only the average volume of individual lesion (over 10 cc) was negatively related with survival time according to Kaplan-Meier method. Cox-proportional hazard ratio of each variable was 1.1559 for the number of lesions, 1.0005 for the average volume of lesions, 0.0894 for the numbers of repeated GKRS, and 0.5970 for the interval of development of new lesions. **CONCLUSION:** This study showed extended survival time in group A compared with group B. Our result supports that multiple GKRS is of value in extending the survival time in patients with multiple metachronous brain metastases, and that the number of the lesions and the frequency of development of new lesions are not an obstacle in treating patients with GKRS.

[362] Stereotactic radiosurgery for the treatment of brain metastases: impact of cerebral disease burden on survival.

British journal of neurosurgery. 2012;26(5):674-8

Banfill KE, Bownes PJ, St Clair SE, Loughrey C, Hatfield P

PMID: 22747250 DOI: 10.3109/02688697.2012.690913

Stereotactic radiosurgery (SRS) for brain metastases has been carried out at the Leeds Gamma Knife Centre since March 2009. The aim of this study was to examine the outcomes and toxicity in our initial cohort of patients. The medical records of patients with brain metastases referred to the Leeds Gamma Knife Centre between March 2009 and July 2010 were retrospectively reviewed. Data on survival, primary tumour, Karnofsky performance status, time from diagnosis to identification of brain metastases, previous treatment for brain metastases and results of staging prior to SRS were recorded. Patients were followed up with regular magnetic resonance imaging of the brain for a minimum of 6 months and data on toxicity and oral steroid dose were recorded. Statistical analysis was carried out using SPSS v14.0. Survival curves were compared using the Log Rank test. Fifty eight patients (19 male) had a median survival of 50.4 weeks (95% CI, 32.6-68.2 weeks). Lung (36%) and breast (27%) were the most common primary tumours. Patients with a total volume of metastases treated < 5000 mm³ (p = 0.007) or between 5000 mm³ and 10,000 mm³ (p = 0.01) had significantly improved survival compared with patients with a total treated volume > 10,000 mm³. In addition, largest treated lesion < 5000 mm³ was a positive prognostic factor. Patients with a single metastasis did not survive significantly longer than those with multiple metastases. Steroid dose dropped significantly after SRS (p < 0.01) and was the same or less in 91% of patients. There were only three cases of grade 3 toxicity. Our study reports survival comparable with other series on radiosurgery and demonstrates a significant decrease in steroid dose following treatment. It also shows that the size of the largest treated metastasis and total volume of metastatic disease seemed a better predictor of outcome than number of metastases treated.

[363] Leptomeningeal seeding in patients with brain metastases treated by gamma knife radiosurgery.

Journal of neuro-oncology. 2012;109(2):293-9

Jo KI, Lim DH, Kim ST, Im YS, Kong DS, Seol HJ, Nam DH, Lee JI

PMID: 22610938 DOI: 10.1007/s11060-012-0892-6

To characterize the development of leptomeningeal seeding (LMS) in patients

with brain metastases after gamma knife radiosurgery (GKRS). Eight hundred and twenty-seven patients that underwent GKRS as a part of an initial treatment plan for brain metastases between January 2002 and December 2010 were included in the study. Six hundred and fifty patients were treated with GKRS alone and 177 patients received GKRS combined with upfront whole brain radiation therapy (WBRT). Actuarial curves for overall survival (OS) and the development of LMS were plotted using the Kaplan-Meier method. Median overall survival for all patients was 55 weeks (95% CI, 47.8-62.2), and the overall incidence of LMS was 5.3%. The actuarial rates for LMS at 6 and 12 months were 3.1 and 5.8, respectively. Uni- and multivariate analysis suggested that breast cancer and a large number of metastases (n ≥ 4) are significant risk factors of LMS (P < 0.05). Regarding treatment modalities, the addition of WBRT was found to have a significant impact on lowering the risk of LMS by multivariate analysis (P = 0.045). LMS is an important pattern of CNS failure. The risk of LMS following GKRS may be associated with multiple lesions, breast cancer, and the omission of WBRT. Additional data from large-scale, randomized controlled trials are required to identify risk factors associated with the LMS more accurately.

[364] Stereotactic radiosurgery using the Leksell Gamma Knife Perfexion unit in the management of patients with 10 or more brain metastases.

Journal of neurosurgery. 2012;117(2):237-45

Grandhi R, Kondziolka D, Monaco EA 3rd, Kano H, Niranjan A, Flickinger JC, Lunsford LD

PMID: 22631694 DOI: 10.3171/2012.4.JNS11870

OBJECT: To better establish the role of stereotactic radiosurgery (SRS) in treating patients with 10 or more intracranial metastases, the authors assessed clinical outcomes and identified prognostic factors associated with survival and tumor control in patients who underwent radiosurgery using the Leksell Gamma Knife Perfexion (LGK PFX) unit. **METHODS:** The authors retrospectively reviewed data in all patients who had undergone LGK PFX surgery to treat 10 or more brain metastases in a single session at the University of Pittsburgh. Posttreatment imaging studies were used to assess tumor response, and patient records were reviewed for clinical follow-up data. All data were collected by a neurosurgeon who had not participated in patient care. **RESULTS:** Sixty-one patients with 10 or more brain metastases underwent SRS for the treatment of 806 tumors (mean 13.2 lesions). Seven patients (11.5%) had no previous therapy. Stereotactic radiosurgery was the sole prior treatment modality in 8 patients (13.1%), 22 (36.1%) underwent whole-brain radiation therapy (WBRT) only, and 16 (26.2%) had prior SRS and WBRT. The total treated tumor volume ranged from 0.14 to 40.21 cm³, and the median radiation dose to the tumor margin was 16 Gy. The median survival following SRS for 10 or more brain metastases was 4 months, with improved survival in patients with fewer than 14 brain metastases, a nonmelanomatous primary tumor, controlled systemic disease, a better Karnofsky Performance Scale score, and a lower recursive partitioning analysis (RPA) class. Prior cerebral treatment did not influence survival. The median survival for a patient with fewer than 14 brain metastases, a nonmelanomatous primary tumor, and controlled systemic disease was 21.0 months. Sustained local tumor control was achieved in 81% of patients. Prior WBRT predicted the development of new adverse radiation effects. **CONCLUSIONS:** Stereotactic radiosurgery safely and effectively treats intracranial disease with a high rate of local control in patients with 10 or more brain metastases. In patients with fewer metastases, a nonmelanomatous primary lesion, controlled systemic disease, and a low RPA class, SRS may be most valuable. In selected patients, it can be considered as first-line treatment.

[365] Subclassification of recursive partitioning analysis Class II patients with brain metastases treated radiosurgically.

International journal of radiation oncology, biology, physics. 2012;83(5):1399-405

Yamamoto M, Sato Y, Serizawa T, Kawabe T, Higuchi Y, Nagano O, Barford BE, Ono J, Kasuya H, Urakawa Y

PMID: 22209155 DOI: 10.1016/j.ijrobp.2011.10.018

PURPOSE: Although the recursive partitioning analysis (RPA) class is generally

used for predicting survival periods of patients with brain metastases (METs), the majority of such patients are Class II and clinical factors vary quite widely within this category. This prompted us to divide RPA Class II patients into three subclasses. **METHODS AND MATERIALS:** This was a two-institution, institutional review board-approved, retrospective cohort study using two databases: the Mito series (2,000 consecutive patients, comprising 787 women and 1,213 men; mean age, 65 years [range, 19-96 years]) and the Chiba series (1,753 patients, comprising 673 female and 1,080 male patients; mean age, 65 years [range, 7-94 years]). Both patient series underwent Gamma Knife radiosurgery alone, without whole-brain radiotherapy, for brain METs during the same 10-year period, July 1998 through June 2008. The Cox proportional hazard model with a step-wise selection procedure was used for multivariate analysis. **RESULTS:** In the Mito series, four factors were identified as favoring longer survival: Karnofsky Performance Status (90% to 100% vs. 70% to 80%), tumor numbers (solitary vs. multiple), primary tumor status (controlled vs. not controlled), and non-brain METs (no vs. yes). This new index is the sum of scores (0 and 1) of these four factors: RPA Class II-a, score of 0 or 1; RPA Class II-b, score of 2; and RPA Class II-c, score of 3 or 4. Next, using the Chiba series, we tested whether our index is valid for a different patient group. This new system showed highly statistically significant differences among subclasses in both the Mito series and the Chiba series ($p < 0.001$ for all subclasses). In addition, this new index was confirmed to be applicable to Class II patients with four major primary tumor sites, that is, lung, breast, alimentary tract, and urogenital organs. **CONCLUSIONS:** Our new grading system should be considered when designing future clinical trials involving brain MET patients.

[366] Treatment of five or more brain metastases with stereotactic radiosurgery. *International journal of radiation oncology, biology, physics.* 2012;83(5):1394-8
Hunter GK, Suh JH, Reuther AM, Vogelbaum MA, Barnett GH, Angelov L, Weil RJ, Neyman G, Chao ST
PMID: 22209150 DOI: 10.1016/j.ijrobp.2011.10.026

PURPOSE: To examine the outcomes of patients with five or more brain metastases treated in a single session with stereotactic radiosurgery (SRS). **METHODS AND MATERIALS:** Sixty-four patients with brain metastases treated with SRS to five or more lesions in a single session were reviewed. Primary disease type, number of lesions, Karnofsky performance score (KPS) at SRS, and status of primary and systemic disease at SRS were included. Patients were treated using dosing as defined by Radiation Therapy Oncology Group Protocol 90-05, with adjustments for critical structures. We defined prior whole-brain radiotherapy (WBRT) as WBRT completed >1 month before SRS and concurrent WBRT as WBRT completed within 1 month before or after SRS. Kaplan-Meier estimates and Cox proportional hazard regression were used to determine which patient and treatment factors predicted overall survival (OS). **RESULTS:** The median OS after SRS was 7.5 months. The median KPS was 80 (range, 60-100). A KPS of ≥ 80 significantly influenced OS (median OS, 4.8 months for KPS ≤ 70 vs. 8.8 months for KPS ≥ 80 , $p = 0.0097$). The number of lesions treated did not significantly influence OS (median OS, 6.6 months for eight or fewer lesions vs. 9.9 months for more than eight, $p =$ nonsignificant). Primary site histology did not significantly influence median OS. On multivariate Cox modeling, KPS and prior WBRT significantly predicted for OS. Whole-brain radiotherapy before SRS compared with concurrent WBRT significantly influenced survival, with a risk ratio of 0.423 (95% confidence interval 0.191-0.936, $p = 0.0338$). No significant differences were observed when no WBRT was compared with concurrent WBRT or when the no WBRT group was compared with prior WBRT. A KPS of ≤ 70 predicted for poorer outcomes, with a risk ratio of 2.164 (95% confidence interval 1.157-4.049, $p = 0.0157$). **CONCLUSIONS:** Stereotactic radiosurgery to five or more brain lesions is an effective treatment option for patients with metastatic cancer, especially for patients previously treated with WBRT. A KPS of ≥ 80 predicts for an improved outcome.

[367] Implications of Identifying Additional Cerebral Metastases during Gamma Knife Radiosurgery.

International journal of surgical oncology. 2012;2012:748284
Patel TR, Ozturk AK, Knisely JP, Chiang VL
PMID: 22312543 DOI: 10.1155/2012/748284

INTRODUCTION: Gamma Knife radiosurgery (GK-SRS) is commonly used to treat cerebral metastases. Although additional intracranial metastases are often found on the day of GK-SRS, the significance of finding them is unknown. **METHODS:** A retrospective review of 133 patients undergoing GK-SRS for cerebral metastases was performed. The change in number of metastases detected between initial referral magnetic resonance imaging (MRI) and subsequent treatment MRI was quantified. Multivariate and Kaplan-Meier analyses were employed to examine the significance of identifying additional lesions. Results. Additional lesions were identified in 41% of patients. An increasing number of metastases on referral MRI ($P = 0.001$) and the presence of progressive systemic disease ($P = 0.003$) were predictive of identifying additional metastases. Median survival was 6.9 months for patients with additional metastases, compared to 12.1 months for patients without additional metastases (hazard ratio 1.56, $P = 0.021$). **CONCLUSIONS:** Identifying additional metastases on the day of GK-SRS may add important prognostic information.

[368] Analysis of 2000 cases treated with gamma knife surgery: validating eligibility criteria for a prospective multi-institutional study of stereotactic radiosurgery alone for treatment of patients with 1-10 brain metastases (JLGK0901) in Japan.

Journal of radiosurgery and SBRT. 2012;2(1):19-27
Serizawa T, Higuchi Y, Nagano O, Sato Y, Yamamoto M, Ono J, Saeki N, Miyakawa A, Hirai T
PMID: 29296339 DOI:

OBJECTIVE: The Japan Leksell Gamma Knife (JLGK) Society has conducted a prospective multi-institute study (JLGK0901, UNIN000001812) for selected patients in order to prove the effectiveness of stereotactic radiosurgery (SRS) alone using the gamma knife (GK) for 1-10 brain lesions. Herein, we verify the validity of 5 major patient selection criteria for the JLGK0901 trial. **MATERIALS AND METHODS:** Between 1998 and 2010, 2246 consecutive cases with 10352 brain metastases treated with GK were analyzed to determine the validity of the following 5 major JLGK0901 criteria; 1) 1-10 brain lesions, 2) less than 10 cm³ volume of the largest tumor, 3) no more than 15 cm³ total tumor volume, 4) no cerebrospinal fluid (CSF) dissemination, 5) Karnofsky performance status (KPS) score ≥ 70 . **RESULTS:** For cases with >10 brain metastases, salvage treatments for new lesions were needed more frequently. The tumor control rate for lesions larger than 10 cm³ was significantly lower than that of tumors <10 cm³. Overall, neurological and qualitative survivals (OS, NS, QS) of cases with >15 cm³ total tumor volume or positive magnetic resonance imaging findings of CSF were significantly poorer. Outcomes in cases with KPS <70 were significantly poorer in terms of OS. **CONCLUSION:** Our retrospective results of 2246 GK-treated cases verified the validity of the 5 major JLGK0901 criteria. The inclusion criteria for the JLGK0901 study are apparently good indications for SRS.

[369] How many metastases can be treated with radiosurgery?

Progress in neurological surgery. 2012;25:261-72
Yamamoto M, Kawabe T, Barford BE
PMID: 22236687 DOI: 10.1159/000331199

We describe postradiosurgical treatment outcomes of our consecutive series of 1,676 patients (654 females and 1,022 males, mean age 63 years, range 19-92 years) who underwent Gamma Knife radiosurgery (GKRS) for brain metastases, focusing particularly on GKRS for multiple lesions. The most common primary cancer was lung (1,057; 63.1%), followed by alimentary tract (198; 11.8%), breast (180; 10.7%), uro-genital (113; 6.7%) and others (128; 7.6%). Mean and median lesion numbers were 7 and 3, respectively, range 1-85. The overall median survival times were 9.0 months in females and 5.9 in males after GKRS ($p < 0.0001$). The

Kaplan-Meier method was used to assess tumor numbers by group: 1-4, 5-9, 10-14, 15-19, 20-24, 25-29, 30-39 and ≥ 40 . The post-GKRS median survival times were 8.3, 5.3, 6.9, 5.2, 5.6, 3.0, 5.3 and 4.3 months, respectively ($p < 0.0001$). Also, the Kaplan-Meier method was used to compare 15 pairs of groups based on tumor numbers: 1 vs. ≥ 2 , ≤ 2 vs. ≥ 3 , ≤ 3 vs. ≥ 4 , ---, and ≤ 15 vs. ≥ 16 . In each of the 15 pairs, the median survival times of patients with lower tumor numbers were significantly longer than those of patients with higher tumor numbers ($p < 0.0001$). Furthermore, 14 other pairs of groups, based on tumor numbers, were also assessed by this method: 1 vs. 2, 2 vs. 3, 3 vs. 4, ---, and 14 vs. 15. Among the 14 pairs, only the 1 vs. 2 pair showed a significant median survival time difference ($p = 0.0002$); no significant differences were detected for the other 13 pairs. Although tumor number was demonstrated to have a significant impact on the duration of survival, approximately 85% of patients with brain metastasis died of causes other than brain disease progression, regardless of tumor number.

[370] The effect of targeted agents on outcomes in patients with brain metastases from renal cell carcinoma treated with Gamma Knife surgery.

Journal of neurosurgery. 2012;116(5):978-83

Cochran DC, Chan MD, Aklilu M, Lovato JF, Alphonse NK, Bourland JD, Urbanic JJ, McMullen KP, Shaw EG, Tatter SB, Ellis TL

PMID: 22385005 DOI: 10.3171/2012.2.JNS111353

OBJECT: Gamma Knife surgery (GKS) has been reported as an effective modality for treating brain metastases from renal cell carcinoma (RCC). The authors aimed to determine if targeted agents such as tyrosine kinase inhibitors, mammalian target of rapamycin inhibitors, and bevacizumab affect the patterns of failure of RCC after GKS. **METHODS:** Between 1999 and 2010, 61 patients with brain metastases from RCC were treated with GKS. A median dose of 20 Gy (range 13-24 Gy) was prescribed to the margin of each metastasis. Kaplan-Meier analysis was used to determine local control, distant failure, and overall survival rates. Cox proportional hazard regression was performed to determine the association between disease-related factors and survival. **RESULTS:** Overall survival at 1, 2, and 3 years was 38%, 17%, and 9%, respectively. Freedom from local failure at 1, 2, and 3 years was 74%, 61%, and 40%, respectively. The distant failure rate at 1, 2, and 3 years was 51%, 79%, and 89%, respectively. Twenty-seven percent of patients died of neurological disease. The median survival for patients receiving targeted agents ($n = 24$) was 16.6 months compared with 7.2 months ($n = 37$) for those not receiving targeted therapy ($p = 0.04$). Freedom from local failure at 1 year was 93% versus 60% for patients receiving and those not receiving targeted agents, respectively ($p = 0.01$). Multivariate analysis showed that the use of targeted agents (hazard ratio 3.02, $p = 0.003$) was the only factor that predicted for improved survival. Two patients experienced post-GKS hemorrhage within the treated volume. **CONCLUSIONS:** Targeted agents appear to improve local control and overall survival in patients treated with GKS for metastatic RCC.

[371] Gamma knife stereotactic radiosurgery as salvage therapy after failure of whole-brain radiotherapy in patients with small-cell lung cancer.

International journal of radiation oncology, biology, physics. 2012;83(1):e53-9

Harris S, Chan MD, Lovato JF, Ellis TL, Tatter SB, Bourland JD, Munley MT, deGuzman AF, Shaw EG, Urbanic JJ, McMullen KP

PMID: 22342297 DOI: 10.1016/j.ijrobp.2011.11.059

PURPOSE: Radiosurgery has been successfully used in selected cases to avoid repeat whole-brain irradiation (WBI) in patients with multiple brain metastases of most solid tumor histological findings. Few data are available for the use of radiosurgery for small-cell lung cancer (SCLC). **METHODS AND MATERIALS:** Between November 1999 and June 2009, 51 patients with SCLC and previous WBI and new brain metastases were treated with GammaKnife stereotactic radiosurgery (GKSRS). A median dose of 18 Gy (range, 10-24 Gy) was prescribed to the margin of each metastasis. Patients were followed with serial imaging. Patient electronic records were reviewed to determine disease-related factors and clinical outcomes after GKSRS. Local and distant brain failure rates, overall survival, and likelihood of neurologic death were determined based on imaging

results. The Kaplan-Meier method was used to determine survival and local and distant brain control. Cox proportional hazard regression was performed to determine strength of association between disease-related factors and survival.

RESULTS: Median survival time for the entire cohort was 5.9 months. Local control rates at 1 and 2 years were 57% and 34%, respectively. Distant brain failure rates at 1 and 2 years were 58% and 75%, respectively. Fifty-three percent of patients ultimately died of neurologic death. On multivariate analysis, patients with stable (hazard ratio [HR] = 2.89) or progressive (HR = 6.98) extracranial disease (ECD) had worse overall survival than patients without evidence of ECD ($p = 0.00002$). Concurrent chemotherapy improved local control (HR = 89; $p = 0.006$).

CONCLUSIONS: GKSRS represents a feasible salvage option in patients with SCLC and brain metastases for whom previous WBI has failed. The status of patients' ECD is a dominant factor predictive of overall survival. Local control may be inferior to that seen with other cancer histological results, although the use of concurrent chemotherapy may help to improve this.

[372] Radiosurgery for large brain metastases.

International journal of radiation oncology, biology, physics. 2012;83(1):113-20

Han JH, Kim DG, Chung HT, Paek SH, Park CK, Jung HW

PMID: 22019247 DOI: 10.1016/j.ijrobp.2011.06.1965

PURPOSE: To determine the efficacy and safety of radiosurgery in patients with large brain metastases treated with radiosurgery. **PATIENTS AND METHODS:** Eighty patients with large brain metastases (> 14 cm³) were treated with radiosurgery between 1998 and 2009. The mean age was 59 +/- 11 years, and 49 (61.3%) were men. Neurologic symptoms were identified in 77 patients (96.3%), and 30 (37.5%) exhibited a dependent functional status. The primary disease was under control in 36 patients (45.0%), and 44 (55.0%) had a single lesion. The mean tumor volume was 22.4 +/- 8.8 cm³, and the mean marginal dose prescribed was 13.8 +/- 2.2 Gy. **RESULTS:** The median survival time from radiosurgery was 7.9 months (95% confidence interval [CI], 5.343-10.46), and the 1-year survival rate was 39.2%. Functional improvement within 1-4 months or the maintenance of the initial independent status was observed in 48 (60.0%) and 20 (25.0%) patients after radiosurgery, respectively. Control of the primary disease, a marginal dose of ≥ 11 Gy, and a tumor volume ≥ 26 cm³ were significantly associated with overall survival (hazard ratio, 0.479; $p = .018$; 95% CI, 0.261-0.880; hazard ratio, 0.350; $p = .004$; 95% CI, 0.171-0.718; hazard ratio, 2.307; $p = .006$; 95% CI, 1.274-4.180, respectively). Unacceptable radiation-related toxicities (Radiation Toxicity Oncology Group central nervous system toxicity Grade 3, 4, and 5 in 7, 6, and 2 patients, respectively) developed in 15 patients (18.8%). **CONCLUSION:** Radiosurgery seems to have a comparable efficacy with surgery for large brain metastases. However, the rate of radiation-related toxicities after radiosurgery should be considered when deciding on a treatment modality.

[373] Prognostic factors for survival in patients treated with stereotactic radiosurgery for recurrent brain metastases after prior whole brain radiotherapy.

International journal of radiation oncology, biology, physics. 2012;83(1):303-9

Caballero JA, Sneed PK, Lamborn KR, Ma L, Denduluri S, Nakamura JL, Barani IJ, McDermott MW

PMID: 22079723 DOI: 10.1016/j.ijrobp.2011.06.1987

PURPOSE: To evaluate prognostic factors for survival after stereotactic radiosurgery (SRS) for new, progressive, or recurrent brain metastases (BM) after prior whole brain radiotherapy (WBRT). **METHODS AND MATERIALS:** Patients treated between 1991 and 2007 with Gamma Knife SRS for BM after prior WBRT were retrospectively reviewed. Potential prognostic factors were analyzed overall and by primary site using univariate and stepwise multivariate analyses and recursive partitioning analysis, including age, Karnofsky performance status (KPS), primary tumor control, extracranial metastases, number of BM treated, total SRS target volume, and interval from WBRT to SRS. **RESULTS:** A total of 310 patients were analyzed, including 90 breast, 113 non-small-cell lung, 31 small-cell lung, 42 melanoma, and 34 miscellaneous patients. The median age was 56, KPS 80, number of BM treated 3, and interval from WBRT to SRS 8.1 months; 76% had

controlled primary tumor and 60% had extracranial metastases. The median survival was 8.4 months overall and 12.0 vs. 7.9 months for single vs. multiple BM treated ($p = 0.001$). There was no relationship between number of BM and survival after excluding single-BM patients. On multivariate analysis, favorable prognostic factors included age <50 , smaller total target volume, and longer interval from WBRT to SRS in breast cancer patients; smaller number of BM, KPS >60 , and controlled primary in non-small-cell lung cancer patients; and smaller total target volume in melanoma patients. **CONCLUSIONS:** Among patients treated with salvage SRS for BM after prior WBRT, prognostic factors appeared to vary by primary site. Although survival time was significantly longer for patients with a single BM, the median survival time of 7.9 months for patients with multiple BM seems sufficiently long for salvage SRS to appear to be worthwhile, and no evidence was found to support the use of a cutoff for number of BM appropriate for salvage SRS.

[374] Intracranial relapse rates and patterns, and survival trends following post-resection cavity radiosurgery for patients with single intracranial metastases.

Journal of neuro-oncology. 2012;108(1):141-6

Ogiwara H, Kalakota K, Rakhra SS, Helenowski IB, Marymont MH, Kalapurakal JA, Mehta MP, Levy RB, Chandler JP

PMID: 22426925 DOI: 10.1007/s11060-012-0808-5

The objective of this study is to evaluate the patterns of relapse and survival trends in patients with single brain metastases treated with post-operative adjuvant Gamma knife stereotactic radiosurgery (GKS) without whole brain radiotherapy (WBRT). Retrospective analysis of all consecutive patients who underwent GKS to the tumor cavity following resection of solitary brain metastasis was performed at a single institution. Between March 2001 and June 2010, 56 patients underwent GKS to the resection cavity following resection of intracranial metastases; no patient received pre- or post-operative WBRT as an adjuvant (salvage WBRT was permissible). The mean marginal dose was 17.1 Gy (range 14-20 Gy). The mean follow-up period was 24 months (range 3-99 months). Five patients (8.9%) had local recurrence in the immediate vicinity of the resection cavity, qualifying as "local failures", and 21 (37.5%) recurred at distant intracranial sites. Median intracranial recurrence free survival was 13 months. Median overall survival was 20.5 months. Salvage interventions were required in 26 patients, and included repeat radiosurgery in 17 patients, further surgery in two patients, and salvage WBRT in eight (14.3%); two of whom had also been locally salvaged with repeat radiosurgery patients. As expected, avoidance of WBRT results in a high rate of intracranial failure (26/56 patients, 46%), even in well-selected patients with only single brain metastases. As anticipated, the majority of failures (21, 37.5%) are "distant intracranial", and in this well-selected cohort the local failure rate is low (5/56 patients, $<9\%$). All patients failing intracranially (46%) are potential candidates for salvage therapies, but WBRT as salvage was utilized in only 14.3% of patients. The median intracranial relapse-free was 13 months and overall survival was 20.5 months.

[375] Effect of tumor subtype on survival and the graded prognostic assessment for patients with breast cancer and brain metastases.

International journal of radiation oncology, biology, physics. 2012;82(5):2111-7

Sperduto PW, Kased N, Roberge D, Xu Z, Shanley R, Luo X, Sneed PK, Chao ST, Weil RJ, Suh J, Bhatt A, Jensen AW, Brown PD, Shih HA, Kirkpatrick J, Gaspar LE, Fiveash JB, Chiang V, Knisely JP, Sperduto CM, Lin N, Mehta M
PMID: 21497451 DOI: 10.1016/j.ijrobp.2011.02.027

PURPOSE: The diagnosis-specific Graded Prognostic Assessment (GPA) was published to clarify prognosis for patients with brain metastases. This study refines the existing Breast-GPA by analyzing a larger cohort and tumor subtype. **METHODS AND MATERIALS:** A multi-institutional retrospective database of 400 breast cancer patients treated for newly diagnosed brain metastases was generated. Prognostic factors significant for survival were analyzed by multivariate Cox regression and recursive partitioning analysis (RPA). Factors were weighted by the magnitude of their regression coefficients to define the GPA index.

RESULTS: Significant prognostic factors by multivariate Cox regression and RPA were Karnofsky performance status (KPS), HER2, ER/PR status, and the interaction between ER/PR and HER2. RPA showed age was significant for patients with KPS 60 to 80. The median survival time (MST) overall was 13.8 months, and for GPA scores of 0 to 1.0, 1.5 to 2.0, 2.5 to 3.0, and 3.5 to 4.0 were 3.4 ($n = 23$), 7.7 ($n = 104$), 15.1 ($n = 140$), and 25.3 ($n = 133$) months, respectively ($p < 0.0001$). Among HER2-negative patients, being ER/PR positive improved MST from 6.4 to 9.7 months, whereas in HER2-positive patients, being ER/PR positive improved MST from 17.9 to 20.7 months. The log-rank statistic (predictive power) was 110 for the Breast-GPA vs. 55 for tumor subtype. **CONCLUSIONS:** The Breast-GPA documents wide variation in prognosis and shows clear separation between subgroups of patients with breast cancer and brain metastases. This tool will aid clinical decision making and stratification in clinical trials. These data confirm the effect of tumor subtype on survival and show the Breast-GPA offers significantly more predictive power than the tumor subtype alone.

[376] Early significant tumor volume reduction after radiosurgery in brain metastases from renal cell carcinoma results in long-term survival.

International journal of radiation oncology, biology, physics. 2012;82(5):1749-55

Kim WH, Kim DG, Han JH, Paek SH, Chung HT, Park CK, Kim CY, Kim YH, Kim JW, Jung HW

PMID: 21640509 DOI: 10.1016/j.ijrobp.2011.03.044

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 cm³ (range, 0.01-35.1 cm³), 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.

[377] Salvage treatment of distant recurrent brain metastases with Gamma Knife surgery.

Acta neurochirurgica. 2012;154(2):285-90

Hanssens P, Karlsson B, Vashu R, Yeo TT, Beute G

PMID: 22146846 DOI: 10.1007/s00701-011-1240-x

BACKGROUND: The aim of the study was to analyze the results following salvage Gamma Knife(R) surgery (GKS) for distant recurrent brain metastases in patients previously treated with GKS for brain metastases. **METHODS:** Survival time and freedom from new distant recurrences (DR) were studied in 251 patients treated with salvage GKS for brain metastases that had developed following a first GKS. The patients were followed prospectively and the results related to a number of patient parameters as well as the results following the first GKS. **RESULTS:** The median survival time was 9.6 months, and the median time of freedom from developing DR was 7.5 months after salvage GKS. The survival time was unrelated to age, gender, prior WBRT, and primary disease. It was significantly longer in patients with a single DR at salvage GKS as compared to those with multiple ones (16 versus 8.3 months). Patients with 2-4 DRs lived longer than those with

>4 lesions, 10 versus 5.8 months. The survival was significantly longer following salvage GKS as compared to following the first GKS. The prognosis of a patient with DR may therefore be less ominous than previously assumed. A classification system for DRs based on their clinical impact and treatability is therefore suggested. **CONCLUSIONS:** The longer survival time following salvage GKS as compared to following the first GKS suggests that many patients benefit from salvage GKS. A classification system of DR is suggested to estimate its clinical impact.

[378] Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases.

Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(4):419-25

Sperduto PW, Kased N, Roberge D, Xu Z, Shanley R, Luo X, Sneed PK, Chao ST, Weil RJ, Suh J, Bhatt A, Jensen AW, Brown PD, Shih HA, Kirkpatrick J, Gaspar LE, Fiveash JB, Chiang V, Knisely JP, Sperduto CM, Lin N, Mehta M
PMID: 22203767 DOI: 10.1200/JCO.2011.38.0527

PURPOSE: Our group has previously published the Graded Prognostic Assessment (GPA), a prognostic index for patients with brain metastases. Updates have been published with refinements to create diagnosis-specific Graded Prognostic Assessment indices. The purpose of this report is to present the updated diagnosis-specific GPA indices in a single, unified, user-friendly report to allow ease of access and use by treating physicians. **METHODS:** A multi-institutional retrospective (1985 to 2007) database of 3,940 patients with newly diagnosed brain metastases underwent univariate and multivariate analyses of prognostic factors associated with outcomes by primary site and treatment. Significant prognostic factors were used to define the diagnosis-specific GPA prognostic indices. A GPA of 4.0 correlates with the best prognosis, whereas a GPA of 0.0 corresponds with the worst prognosis. **RESULTS:** Significant prognostic factors varied by diagnosis. For lung cancer, prognostic factors were Karnofsky performance score, age, presence of extracranial metastases, and number of brain metastases, confirming the original Lung-GPA. For melanoma and renal cell cancer, prognostic factors were Karnofsky performance score and the number of brain metastases. For breast cancer, prognostic factors were tumor subtype, Karnofsky performance score, and age. For GI cancer, the only prognostic factor was the Karnofsky performance score. The median survival times by GPA score and diagnosis were determined. **CONCLUSION:** Prognostic factors for patients with brain metastases vary by diagnosis, and for each diagnosis, a robust separation into different GPA scores was discerned, implying considerable heterogeneity in outcome, even within a single tumor type. In summary, these indices and related worksheet provide an accurate and facile diagnosis-specific tool to estimate survival, potentially select appropriate treatment, and stratify clinical trials for patients with brain metastases.

[379] Clinical outcome of central nervous system metastases from breast cancer: differences in survival depending on systemic treatment.

Journal of neuro-oncology. 2012;106(2):303-13

Kim HJ, Im SA, Keam B, Kim YJ, Han SW, Kim TM, Oh DY, Kim JH, Lee SH, Chie EK, Han W, Kim DW, Kim TY, Noh DY, Heo DS, Park IA, Bang YJ, Ha SW
PMID: 21938531 DOI: 10.1007/s11060-011-0664-8

Central nerve system (CNS) metastases are a feared complication of breast cancer and are associated with poor prognosis. The purpose of this study is to investigate the clinical characteristics of CNS metastases and to clarify the prognostic factors after CNS metastases in breast cancer at a single institution over a long time period. We retrospectively reviewed the medical records of breast cancer patients diagnosed at Seoul National University Hospital from 1981 to 2009 and identified the patients who experienced CNS metastases. We collected the data, including demographics, clinico-pathologic characteristics, dates of diagnosis of original breast cancer and subsequent metastases, and date of death, and correlated the findings with the clinical outcome. A total of 400 patients were identified, of

whom 17 (4.3%) were diagnosed with CNS metastases and primary breast cancer concurrently and 383 (95.7%) experienced CNS metastases subsequent to the diagnosis of primary breast cancer. Further, 318 patients (79.5%) had only brain parenchymal metastases, 30 (7.5%) had only leptomeningeal metastases, and 52 (13%) had both. After the diagnosis of CNS metastasis, 170 patients (42.5%) received systemic chemotherapy (CTx) and 143 (35.8%) received CTx after whole brain radiation therapy (WBRT). The patients with good performance status (PS), initial CNS metastasis as recurrence, absence of extracranial metastases, non-visceral extracranial metastases, longer interval from the date of primary breast cancer to the date of CNS metastasis, and CTx after WBRT and gamma-knife surgery (GKS), had better outcomes in univariate analyses. In multivariate analysis, good PS, systemic CTx after WBRT, GKS, and longer interval to CNS metastasis, were independent prognostic factors for overall survival after CNS metastases. Our results suggest that appropriate palliative systemic therapy after WBRT or GKS, and adequate palliative treatment via combined modalities are helpful for breast cancer patients, even after the detection of CNS metastases.