Clinical Indications for Gamma Knife Radiosurgery
A Review of the Published Clinical Evidence through 2014

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Introduction

The principle of Gamma Knife radiosurgery implies concentrating radiation within a target in the brain while avoiding radiation of the surrounding healthy tissue. The Gamma Knife achieves this by the mechanical focusing of 192 radiation sources, which allows shaping of an extremely defined irradiated volume in the brain. With modern planning techniques and multiple isocenters virtually any shape of tumor can be matched with high precision radiation. Radiosurgical techniques and particularly the Gamma Knife provide a very steep radiation dose fall-off. The irradiation hits the pathological cells with a locally high concentration of energy while at the same time the neighboring areas of the brain are spared from being affected by the irradiation. This specific gradient of radiation in all three dimensions guarantees that the surrounding brain tissue is exposed to only very little radiation and thereby “protected” against undesired radiation effects.

Radiosurgery is generally carried out in one session under local anesthesia resulting in very low physical stress for the patient. The necessary precision of target localization requires a stereotactic MRI or CT study before radiosurgery and a stereotactic frame fixation (for Linac and Gamma Knife). Radiation doses are expressed as “prescription doses” or “minimum doses” reflecting the dose applied to the tumor periphery. Generally, prescription doses of 15-25 Gy are applied in radiosurgery of brain tumors. In Gamma Knife treatments this minimum dose commonly corresponds to 50% of the maximally applied dose (50% isodose) resulting in an inhomogeneous dose distribution within the tumor often ranging between 36 and 50 Gy. The lack of dose homogeneity is irrelevant for the outcome, because the high dose area lies within the tumor tissue. The stereotactic head frame guarantees the precision needed to protect healthy brain tissue and directs the radiation focus into the target. So far more than a million patients have been treated in worldwide 269 Gamma Knifes centers. The number of annually treated patients has doubled in the last decade and is increasing steadily.

The American College of Radiology and American Society for Radiation Oncology has issued practice guideline for the Performance of Stereotactic Radiosurgery as multidisciplinary approach and defines organization, appropriate staffing, and defines the qualifications and responsibilities of all the involved personnel, including the radiation oncologist, neurosurgeon, and qualified medical physicist including quality assurance issues for the treatment unit, stereotactic accessories, medical imaging, and treatment-planning system 1.
**Gamma Knife Treatment Indications: Overview**

The Gamma Knife technology has enabled neurosurgeons to treat many conditions that are otherwise inaccessible for therapy. The goal of radiosurgery is to maintain quality of life.

In some indications Gamma Knife replaces the open tumor operation. That comprises tumors that are either surgically inaccessible or tumors that had been treated unsuccessfully by conventional surgery, chemotherapy and/or radiation therapy. In other indications Gamma Knife is used as an additive therapy, which enables the conventional surgeon to operate less radically and thereby with a lower complication rate.

It is important to note that Gamma Knife radiosurgery is highly effective even for tumors that are relatively resistant to traditional external beam radiation therapy. Numerous scientific studies have documented the efficacy of radiosurgery against various brain tumors. The majority of brain metastases can be treated successfully using the Gamma Knife with excellent tumor control rates and low associated morbidity. The method was shown to be highly effective even against multiple metastases. Recent results even show a beneficial effect of Gamma Knife treatment in the therapy of gliomas and pediatric and less frequently occurring brain tumors such as pilocytic astrocytoma and ependymoma.

Gamma Knife radiosurgery stops the growth of benign brain tumors such as meningioma. In this indication Gamma Knife radiosurgery is generally used as a complement to open neurosurgical resection in order to allow less invasive operations hereby reducing the otherwise high rate of surgery-related morbidity, intensive care and other ancillary treatments.

A further important group treated with Gamma Knife comprises patients with vestibular Schwannoma (Acoustic Neurinoma), another benign tumor located close to the brain stem. These patients are otherwise treated with highly sophisticated and invasive open surgery. Radiosurgery provides highly efficient local control of these tumors avoiding many of the complications that are associated with open surgery.

Gamma Knife treatments have a very long track record in the treatment of postoperatively recurring both endocrinologically active and inactive pituitary adenoma. In patients with arterio-venous malformations (AVM) of the brain the Gamma Knife is used as an alternative to open surgery. Recent results documented that Gamma Knife radiosurgery provides excellent treatment option for patients with trigeminal neuralgia who fail to respond to medical therapy. Gamma Knife provides a
highly efficient and cost effective alternative in the treatment of Parkinson tremor otherwise treated with highly costly deep brain stimulation.

**Summary Treatment Indications**

- Brain Metastases
- Vestibular Schwannoma (Acoustic Neurinoma)
- Meningioma
- Glioma and other rarer brain tumors
- Pituitary Adenoma
- Arterio-venous malformations (AVM)
- Trigeminal Neuralgia
- Functional Indications (Thalamotomy for tremor etc.)

**Technical Accuracy**

The accuracy of the applied radiation is an inherent part of comparative safety. In the recent Gamma Knife model (Perfexion), the accuracy of the mechanical versus radiation isocenter was found to be 0.05 mm $^2$. Linac planning is negatively affected by a loss of imaging precision due to the requirement of CT based planning and phantom studies with a stereotactic Linac have shown that a CT localized target can be irradiated with a positional accuracy of 0.8 mm in any direction with 95% confidence $^3$.

This technical accuracy is superior to alternative radiosurgery techniques $^4$-$^6$. The closer the prescription dose is matched to the treated target and the steeper the dose gradient around the target, the less normal tissue is irradiated. This matching of the dose to a 3-dimensional target is generally quantified using the conformity index, which reflects the amount of normal tissue within the prescription isodose. A simplified conformity index is the ratio of prescription volume to target volume, which would ideally be 1, if no healthy tissue were irradiated. Polymer gel measurements verified the optimal dose distribution in the most recent Gamma Knife models (Perfexion) with a conformity of 1.17 $^7$. A very recent study examined the radiation dose distributions for treating multiple brain metastases created by Gamma Knife Perfexion in comparison to alternative techniques (Linac single-isocenter volumetric modulated arc radiosurgery) showing that the even the advanced modern stereotactic Linac consistently irradiated a higher amount of normal brain
tissues. These increases were largest for lower isodose levels, with the volumes of normal brain that received 20%-50% and 60%-90% of the prescription dose showing average increases of 403% and 227%, respectively. Radiosurgery quality metrics indicated that the Gamma Knife plan was superior in each case. Extracranial doses vary depending on the technology used. Due to effective shielding, Gamma Knife doses decreased steeply with distance from the treated brain, delivering only 13 mSv at the lower pelvis in comparison to 117 and 132 mSv during CyberKnife treatments. Further reduction of extracranial doses has been shown in the recent Gamma Knife model Perfexion.

In a comparison of three most prominent systems for stereotactic radiosurgery (the Cyberknife system, the Gamma Knife Perfexion and the Novalis system) it was shown that the Gamma Knife showed significantly steeper gradients compared with the Novalis and the Cyberknife system (Gamma Knife vs. Novalis, $p = 0.014$; Gamma Knife vs. Cyberknife, $p = 0.002$). The investigation of inter-target dose interplay effects demonstrated that for multi-target SRS, Gamma Knife PFX spares the normal brain tissue best when compared to CyberKnife, Novalis linear accelerator equipped with a 3.0-mm multi-leaf collimator, and the Varian Truebeam flattening-filter-free linear accelerator. The volumes of normal brain receiving 4 and 12 Gy were higher, and increased more swiftly per target, for Linac-based SRS platforms than Gamma Knife Perfexion. Linac Rapid Arc plans were compared to Gamma Knife plans and dose-related analysis was performed. Rapid Arc plans showed an inferior isotropic falloff and a shallower dose gradient. Both Rapid Arc and Gamma Knife plans resulted in equivalent conformality while plans from GK showed sharper dose gradients resulting in a lower radiation exposure of healthy target surrounding tissue.

The results of prior investigations had shown that the CyberKnife delivered significantly higher peripheral doses to normal tissue than comparable model C Gamma Knife. Chuang, Petti and colleagues investigated the peripheral dose reduction for CyberKnife radiosurgery treatments after the installation of a Linac shielding upgrade and demonstrated that the additional shielding decreased the peripheral dose, expressed as a percentage of the delivered monitor units (MU), by a maximum of 59%. For distances between 30 and 70 cm from the field edge, the additional shielding reduced the peripheral dose by between 20% and 55%, but the CyberKnife peripheral dose still remains higher than doses measured in the center’s previous study for the model C Gamma Knife.
The Leksell Gamma Knife Perfexion (Elekta Instruments AB, Stockholm, Sweden) exceeds the capabilities of previous gamma knife models in terms of treatment efficiency, conformity, and radiation protection. The automated collimator arrangement in the Perfexion makes it possible to produce more complex treatment volumes than with previous models of the gamma knife. This results from the enhanced ability to shape isodose volumes, even for single isocenters. The collimator arrangement and the patient positioning system also allow shorter patient transit times, reducing unwanted radiation exposure during movement between isocenters.

In conclusion, the geometrical accuracy, dose accuracy and the dose gradient around the target and the protection of extra-cranial tissue are superior in the Gamma Knife.

Brain Metastases: General Considerations

More than 185,000 treatments for brain metastases have so far been carried with Gamma Knife radiosurgery. When Pubmed is searched for ‘Gamma Knife and brain metastases’ 1784 publications appear, 101 publications appear for the corresponding search for stereotactic Linac and 37 for CyberKnife. A wide range of retrospective and a prospective studies applying Gamma Knife radiosurgery with more than 6000 patients with brain metastases provide consistent and reproducible results with an average local tumor control between 84% and 97%.

Multivariate analysis indicated that longer freedom from progression was significantly associated with higher radiosurgical dose; local tumor control was superior for metastases treated at minimum doses of 18 Gy or higher. Brain metastases tend to shrink gradually after radiosurgery; the tumor associated perifocal edema disappears after several weeks. Stereotactic radiosurgery is effective even against brain metastases from melanoma or renal cancer that are resistant to fractionated external beam radiation. The tumor volume is the most important limiting factor in radiosurgery. The volume of the irradiated healthy brain in the penumbra of the metastasis increases when larger metastases are treated. This can result in formation of a local edema around the irradiated target, typically 6-9 months after radiosurgery. This effect is generally transient, but may require a steroid medication. Adverse radiation effects are generally seen in larger metastases or non-conformal treatments and are very rare when metastases smaller than 2.5 cm are treated.

While WBRT has been applied for decades as standard therapy in the treatment of brain metastases, recent scientific evidence including multiple randomized studies have now demonstrated a low and insufficient response rate of brain metastases after WBRT, which is reflected by randomized
data showing no life extending effect of WBRT. New metastases develop despite previous WBRT in 23%-50% and in this situation WBRT cannot be repeated. Recent randomized studies have shown that WBRT has a negative impact on cognition, verbal memory and quality of life.

Based on these recent data WBRT does not appear to be sufficiently locally effective, does not prolong the life of cancer patients and is potentially harmful for cognitive functions and quality of life in patients with brain metastases. As a result, WBRT can no longer be considered as safe and effective to provide a reliable and reproducible treatment in patients with brain metastases.

Quality of Life and Treatment of Brain Metastases

Patients receiving stereotactic radiosurgery alone were at significantly lower risk of a decline in learning and memory function by 4 months when compared to patients undergoing additional WBRT. The conclusion from this study was interpreted as level I evidence to support the use of stereotactic radiosurgery alone. Another recent prospective randomized study showed that fractionated cranial irradiation causes a negative impact on health-related quality of life scales particularly due to fatigue and hair loss and causes cognitive dysfunction immediately after the beginning of radiotherapy. Sub-acute radiation effects on verbal memory function are observed, both after therapeutic and prophylactic cranial irradiation. These effects were more pronounced in patients with above-average performance at baseline. A recently published prospective randomized EORTC phase III trial with 359 patients showed that WBRT after surgery or radiosurgery of brain metastases negatively impacted the health-related quality-of-life. Delayed significant CNS toxicity after fractionated radiotherapy is a known phenomenon. It had previously been shown in a smaller prospective study after Gamma Knife treatment for brain metastases that quality of life parameters remained either unchanged or improved in patients who had no evidence of intracranial or extracranial tumor progression. Quality of life was also analyzed as part of the prospective randomized analysis RTOG 95-08 (2004). At 6 months follow-up a statistically significant improvement in clinical performance and decreased steroid use was found in the stereotactic radiosurgery boost treatment group when compared with the patients who had been treated by fractionated radiotherapy only.

Prognostic Factors in Brain Metastases
A multi-institutional retrospective (1985 to 2007) database of 3,940 patients with newly diagnosed brain metastases was studied using univariate and multivariate analyses of prognostic factors associated with outcomes by primary site and treatment. 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 40. Another study analyzed data from 1508 consecutive patients treated with Gamma Knife without upfront whole-brain radiation therapy with 1-10 newly diagnosed brain metastases with a volume of < 10 cm3 and a Karnofsky Performance Scale score > 70. Multivariate analysis revealed significant prognostic factors for overall survival to be sex (poor prognostic factor: male, p < 0.0001), recursive partitioning analysis class (Class I vs. Class II and Class II vs. III, both p < 0.0001), primary site (lung vs. breast, p = 0.0047), and number of tumors (Group A vs. Group B, p < 0.0001). However, no statistically difference was detected between patients with 2-4 tumors (577 cases) and 5-10 tumors (366 cases)(p = 0.1027) 41.

Others confirmed that there was no relationship between number of brain metastases and survival after excluding patients with single brain metastases. 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 brain metastases, KPS >60, and controlled primary in non-small-cell lung cancer patients; and smaller total target volume in melanoma patients 42. The prognostic factors of 400 patients with CNS metastases of breast cancer were reviewed Seoul National University Hospital. The patients with good performance status, non-visceral extracranial metastases, with longer interval from the date of primary breast cancer to the date of CNS metastasis, chemotherapy after WBRT and gamma-knife surgery, had better outcomes in univariate analyses. In multivariate analysis, good performance status, gamma-knife surgery and systemic chemotherapy after WBRT were independent prognostic factors for overall survival after CNS metastases 43.

Treatment safety in competing technologies

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colleagues investigated the peripheral dose reduction for CyberKnife radiosurgery treatments after the installation of a Linac shielding upgrade and demonstrated that the additional shielding decreased the peripheral dose, expressed as a percentage of the delivered monitor units (MU), by a maximum of $59\%$. For distances between 30 and 70 cm from the field edge, the additional shielding reduced the peripheral dose by between $20\%$ and $55\%$, but the CyberKnife peripheral dose still remains higher than doses measured in the center’s previous study for the model C Gamma Knife 14.

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**Comparative Effectiveness: Stereotactic Radiosurgery vs. Open Surgery**  
Three older retrospective 44-46 and one recent prospective randomized study 47 compared the efficacy of radiosurgery of brain metastases with open microsurgery (plus WBRT) which is significantly more invasive that stereotactic radiosurgery. Treatment results did not differ in terms of survival, neurological death rates, and freedom from local recurrence. Radiosurgery was associated with a shorter hospital stay, less frequent and shorter steroid application, and lower frequency of toxicities. The randomized study showed that improved scores for quality of life were seen 6 weeks after radiosurgery 47. As stated in a recent systematic review and evidence-based clinical practice guideline, for smaller metastases the therapeutic effect of Gamma Knife radiosurgery can be considered as equivalent to resection+WBRT (level 3 recommendation) 48.

**Stereotactic Radiosurgery for Brain Metastases in Elderly Patients**  
It was recently shown that SRS for patients aged $\geq 75$ years with brain metastases is an effective and safe treatment modality that appears to improve survival, with outcomes that compare favorably with those reported for younger patients 49.
Similarly Watanabe and colleagues showed in a retrospective case-matched study, that patients with brain metastases who are 80 years of age or older (n=165), are not unfavorable candidates for SRS. In this age group the post-SRS median survival time was shorter than in the cohort aged 65-79 years (5.3 vs. 6.9 months), but this difference was not statistically significant 50.

**Stereotactic Radiosurgery in Larger Metastases**

Larger brain metastases with a clinically relevant mass effect should be removed surgically. Single session radiosurgery in larger metastases should be avoided, since the volume of the irradiated healthy brain in the penumbra of the metastasis increases when larger metastases are treated. As a result, the tumor volume is the primary limiting factor in radiosurgery. A consecutive series of 109 patients with 119 large intracranial metastatic lesions were treated with Gamma Knife surgery (median tumor volume 16.8 cm\(^3\); range 6.0-74.8 cm\(^3\)). Peri-tumoral brain edema as defined on T2-weighted MRI sequences had decreased in 66.4% of lesions was stable in 17.6%, but had progressed in 16.0% 51.

In an attempt to reduce side effects, hypo-fractionated two-session Gamma Knife radiosurgery using 20-30 Gy given in two fractions 3-4 weeks apart was applied for large metastatic brain tumors. (Median tumor volumes 17.8 cm\(^3\) at first GKS and 9.7 cm\(^3\) at second GKS.). The local control rate was 85 % at 6 months and 61 % at 12 months. The overall survival rate after GKS was 63 % at 6 months and 45 % at 12 months 52,53. Alternatively, hypo-fractionated Radiosurgery using 21 Gy in 3 fractions (67%), 24 Gy in 4 fractions (14%) and 30 Gy in 5 fractions (12%) was given in another series resulting in Kaplan-Meier estimates of 1 year local control of 61% . Symptomatic radiation necrosis occurred in 7% 54. In Linac SRS of large brain metastases (>3 cm) a median dose of 24 Gy was applied in 2 to 5 fractions for a median treatment volume of 15.6 mL (range, 10 to 82.7 mL), yielding an actuarial 6-month and 1-year overall survival rates were 22% and 13%, respectively. No patients in this cohort experienced acute or late complications secondary to SRS 55.

**Stereotactic Radiosurgery of the Surgical Resection Cavity**

The risk for local recurrence is high after surgical resection and fractionated radiotherapy is often recommended in order to improve postoperative local control. In order to reduce the known risks of WBRT, however, stereotactic radiosurgery has been applied to the resection cavity. The efficacy of postoperative Gamma Knife surgery to the tumor cavity following gross-total resection of a brain
metastasis has been evaluated in a retrospective review. **Patients with confirmed metastatic disease underwent Gamma Knife surgery to the postoperative resection cavity** following gross-total resection of the tumor (n=47) (lung cancer: 40%, melanoma: 21%, renal cell carcinoma: 15%, breast cancer:15%, gastrointestinal malignancies: 9%). The mean duration between resection and radiosurgery was 15 days (range 2-115 days). The mean volume of the treated cavity was 10.5 cm$^3$ (range 1.75-35.45 cm$^3$), and the mean dose to the cavity margin was 19 Gy. **Local tumor control at the site of the surgical cavity was achieved in 94%**. Another retrospective analysis of 110 patients who had received **Gamma Knife stereotactic radiosurgery to the tumor bed of resected brain metastasis** showed actuarial local control of the cavity at 12 months in 73%. Symptomatic radiation-induced enhancement occurred in 6% of patients and leptomeningeal dissemination in 11%. After stereotactic radiosurgery to the cavity using a lower median dose of 16 Gy delivered to the 50% isodose line median treatment volume 9.2 cm$^3$), a 1-year actuarial local control of 81% was achieved. Leptomeningeal carcinomatosis developed in 14% and was associated with breast histology and infratentorial cavities.

In another group where Gamma knife stereotactic radiosurgery without whole brain radiotherapy was used to treat the tumor cavity following resection of solitary brain metastasis (mean marginal dose 17.1 Gy), only 8.9% had local recurrence in the immediate vicinity of the resection cavity, qualifying as "local failures".

**Salvage Gamma Knife Surgery after Failed WBRT**

The efficacy of Gamma Knife for treating recurrent or new brain metastases after whole-brain radiotherapy (WBRT) in patients with small-cell lung cancer (SCLC) was evaluated as the first-line radiation therapy (n=44). The median duration between WBRT and first GKS was 8.8 months and the tumor control rate was 95.8 % showing that GKS may be an effective option for controlling SCLC-associated brain metastases after WBRT and for preventing neurological death in patients without carcinomatous meningitis. Others showed comparatively low 1-year local control rates of 57% in patients with small-cell lung cancer.

A miscellaneous cohort of 310 patients with brain metastases of various tumor types was treated with Gamma Knife for brain metastases after prior WBRT and showed a median survival of 8.4
months. This series underlines the need for radiosurgical salvage treatment. Similarly, a median overall survival time of 8.2 months and 1-year local control rates of 76.6% were shown after stereotactic radiosurgery salvage treatment for 77 patients with recurrence of brain metastases after whole brain radiotherapy (WBRT). Prescribed dose (>=20 Gy) was an independent predictive factors for local tumor control.

Cognitive Function after Gamma Knife

Previous randomized studies have shown significant improvement in clinical performance and decreased steroid use in a stereotactic radiosurgery boost cohort when compared with the patients who had been treated by fractionated radiotherapy and that WBRT–induced cognitive dysfunction was avoided when SRS was used. A study by Nakazaki and Kano evaluated the mini-mental status examination (MMSE) scores of patients with brain metastases after gamma knife radiosurgery without whole-brain radiation therapy in 119 consecutive patients. In 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. Mental deterioration of patients with large symptomatic metastatic tumors tended to improve after gamma knife.

Short-Term Adverse Effects

A prospective study demonstrated that Gamma Knife is well tolerated with few patients developing major acute effects. The study determined acute complications of intracranial stereotactic radiosurgery, specifically Gamma Knife in 76 eligible patients. At 1 week, 24% complained of minimal scalp numbness, but only 13% had minimal scalp numbness at 1 month and 2% at 2 months, while 13% developed pin site pain at 1 week with a median intensity level of 2 out of 10. By one month, only 3% had pin site pain with a median intensity level of 3 out of 10. There was no pin-site infection at 1 and 2 months. A total of 84% of treated patients returned to work a median of 4 days after SRS.

Imaging Follow-up

DWI/ADC appears to be a practical method for studying the efficacy of radiosurgery and predicting early metastases response progression. A decrease signal on DWI and increased ADC (Apparent diffusion coefficient) values are indicators of good tumor control. DWI (Tumor/white matter) ratios...
between the metastases and the normal, contralateral frontal white matter at each time point was determined in addition to the ADC values for metastases. When using the initial ADCT values of metastases to predict tumor response, sensitivity and specificity were 85.5 and 72.7%, respectively.

**Adverse Radiation Effects**

Yamamoto and associates studied the actual incidence and predictors of delayed complications after Stereotactic Radiosurgery for brain metastases in 167 patients showing 10.2% 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% at the 60th month after GKRS. Among various pre-GKRS clinical factors, univariate analysis demonstrated tumor volume-related factors: largest tumor volume and tumor volume \(<10 \text{ cc} \text{ vs } >10 \text{ cc}\) 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 \(>5 \text{ Gy}\) and \(>12 \text{ Gy}\)).

**Cystic Metastases**

In 111 tumors with cystic components treated with Gamma Knife (Mean target volume 3.3 mL; range, 0.1-23 mL; median prescription dose 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. In order to reduce the volume of irradiated tissue in the treatment of large cystic metastases, Higuchi and colleagues applied the technique of stereotactic aspiration of the cyst with Gamma Knife treatment immediately thereafter. Following aspiration, tumor volume, including the cystic component, decreased from a mean of 20.3 cm\(^3\) to a mean of 10.3 cm\(^3\). At least 20 Gy was delivered to the entire lesion in 24 of 25 cases. Good tumor control was obtained in 16 of 21 cases that could be evaluated during a median follow-up period of 11 months (range 1-27 months); however, reaccumulation of cyst contents was observed in 2 patients who required Ommaya reservoir placement.
Alternatively a “Donut’s shape” radiosurgical treatment planning with a chain-like application of multiple, small-sized isocenters has been used in large cystic intracranial metastases, after which the majority of treated lesions showed significant shrinkage after radiosurgery while no major complications were described 69.

In 2015 Lee, Kim and colleagues retrospectively reviewed the data of 37 cystic brain metastases of 28 patients who were treated with Gamma Knife. Cyst drainage was performed in 8 large lesions before GKRS to decrease the target volume. The mean target volume was 4.8 cm$^3$ (range, 0.3-15.8 cm$^3$) at the time of GKRS, and the mean prescription dose was 16.6 Gy (range, 13-22 Gy). 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) 70.

**Bevacizumab for refractory adverse radiation effects**

Bevacizumab reduces both symptoms and reactive imaging changes in patients with refractory adverse radiation effects (ARE), which are otherwise unresponsive to corticosteroids. In the therapy of treatment refractory ARE Bevacizumab was applied in 29 patients with brain tumors or vascular malformations who had developed clinical and/or imaging evidence of ARE after radiosurgery (average dose of 7.4 mg/kg over a mean of 5.7 weeks at a median of 16 months following SRS). Ninety percent (18/20) with clinically symptomatic ARE had neurological improvement after bevacizumab therapy. Twenty-six patients had a decrease of 62 % of T2/FLAIR volumes and a 50 % decrease in magnetic resonance imaging intravenous contrast enhancement volumes. Symptoms recurred in 11 of the 20 patients after discontinuing therapy 71.

Others showed in a Linac series that bevacizumab treatment offered symptomatic relief in adverse radiation effects, a reduction in steroid requirement, and a dramatic radiographic response. All patients initially receiving steroids had a reduction in steroid requirement, and the vast majority having an improvement in or stability of ARE-associated symptoms. Bevacizumab as a treatment for radiation necrosis of brain metastases post stereotactic radiosurgery 72.
Leptomeningeal seeding

When fractionated whole brain radiotherapy is avoided in the treatment of brain metastases, the risk for leptomeningeal seeding could possibly increase. Among 827 patients that underwent Gamma Knife radiosurgery for brain metastases, the overall incidence of leptomeningeal seeding was 5.3%. The actuarial rates for leptomeningeal seeding at 6 and 12 months were 3.1 and 5.8, respectively. In addition, the risk of leptomeningeal seeding following Gamma Knife may be associated with multiple lesions and breast cancer. After Gamma Knife treatment of non-small cell lung cancer brain metastases, 3.3% developed a leptomeningeal disease.

Stereotactic Radiosurgery of Multiple Brain Metastases

In most patients with multiple metastases, tumors tend to be small and do not affect the patient via local mass effect. Rather than the number of metastases, the total tumor volume appears to have an important influence on the prognosis. In general there is a tendency to treat a larger number of brain metastases in a single radiosurgical session, since numerous studies document high local control after radiosurgical treatment of more than 3 brain metastases. For example, Gamma Knife treatment in patients with 3-6 brain metastases provided actuarial 2-year control rates of 74.3%. In patients with ten or more cerebral metastatic lesions who had undergone Gamma Knife surgery, local control was achieved in 79.5% of the lesions until 6 months after GKS. New lesions appeared in 26.9% patients during the same period. The number of lesions was not a significant predictor of overall survival in 53 patients with ≥ 10 brain metastases treated with Gamma Knife and in another series of 96 patients with 5-15 brain metastases who had been treated using Gamma Knife surgery. 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 overall survival was found to be 4.73 months (range 0.4-41.8 months). Similarly, the median survival following Gamma Knife radiosurgery for 10 or more brain metastases was 4 months in another series with 61 patients, with improved survival in patients with fewer than 14 brain metastases. Similarly, some series indicate a less favorable median survival for patients with more than three or more than seven metastases, but there is no simplistic correlation between the number of metastases and the patient’s prognosis. Hence, an increased number of brain metastases can be an unfavorable factor for longer survival, but the impact on survival time appears to be rather limited. There is increasing evidence that other factors such as the subtype of the primary cancer and the state of the systemic disease are major
The outcome after 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 as demonstrated in 2014 in a prospective observational study comprising 1194 patients [88]. Yamamoto and colleagues recently (2013) published a retrospective case-matched study of patients who had undergone stereotactic radiosurgery without WBRT and demonstrated that the median survival time after radiosurgery was 7.9 months in patients with 1-4 brain metastases (n=548), and 7 months in patients with more than 4 metastases (n=548) (p = 0.01) [89]. This retrospective study suggests that increased tumor number is an unfavorable factor for longer survival. However, the small post-SRS median survival time difference, 0.9 months, between the two groups was not considered clinically meaningful. Similarly, the same group showed that post-SRS median survival times did not differ significantly between patients with 2-9 tumors (1254 patients) and patients with 10 or more tumors (6.8 vs 6.0 months; p = 0.10) [90].

In line with the previously cited findings, Serizawa and Yamamoto published a combined series of 1508 consecutive cases and reported no difference in survival between patients with 2-4 and 5-10 brain metastases [41]. The treatment outcomes of a consecutive series of 1,676 patients who underwent Gamma Knife radiosurgery for brain metastases was studied and 14 pairs of groups, based on tumor numbers, were compared: 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 [91]. In an earlier series of 521 patients treated with Gamma Knife, a similar outcome in terms of overall and neurological survival was found for patients with few (≤3) and many (4-10) brain metastases [92]. Serizawa evaluated the results of gamma knife radiosurgery alone for selected patients with 1-10 brain metastases without prophylactic whole-brain radiation therapy in 778 consecutive cases meeting the JLGK0901 study inclusion. On multivariate analysis, significant poor prognostic factors for overall survival were active systemic disease, poor (<70) initial KPS, and male gender. Neurological survival and qualitative survival at 1 year were 92.7% and 88.2%, respectively. This study revealed that brain lesion number has no effect on overall survival neurological survival.
or qualitative survival, which is anticipated to be confirmed by the JLGK0901 study. Sustained local tumor control after Gamma Knife treatment in patients with 10 or more brain metastases was achieved in 81% of patients.

Previously smaller retrospective studies had shown that number of brain metastases did not have a direct significant impact on survival, which was confirmed after Gamma Knife treatment of patients with breast cancer and renal cancer. In a cohort of 251 patients who had initially been treated with Gamma Knife alone at the MD Anderson Cancer Center it was shown that the number of brain metastases was not predictive of distant brain failure, local control, and overall survival. Similarly, in a retrospective analysis total of 310 patients who had been treated with Gamma Knife radiosurgery after prior WBRT at the Stanford University School of Medicine there was no relationship between the number of brain metastases and survival after excluding patients with single metastases. The prediction of outcome based on the number of lesions was not feasible in another Gamma Knife series with 330 patients.

Patients who had undergone Gamma Knife radiosurgery at the Yonsei University College of Medicine, Seoul (n=323) were divided into groups according to the number of lesions visible on MR images: Median survival was 10 months for patients with 1-5 metastases; 10 months for 6-10 lesions, 13 months for 11-15 lesions and 8 months for patients with more than 15 brain metastases. The difference was not statistically significant.

Similarly, patients with more than 4 brain metastases do not appear to have an inferior outcome in terms of neurological death, repeat SRS, maintenance of good neurological state and radiosurgery-related complications, but several treatment recommendations and practice guidelines limit the number of brain metastases that can be treated with radiosurgery to a virtually arbitrary number of three or four without consideration of tumor volume or diagnostic method. These recommendations are primarily based on level I evidence and hence on the available three randomized studies, where the analysis was limited to patients with less than 3-4 metastases according to the studies’ selection criteria: patients with a larger number of metastases had been excluded from evaluation.
In summary, there is no documented evidence for a lack of radiosurgical efficacy in multiple metastases or for the existence of another superior treatment for this condition.

On the other hand, the total brain metastasis volume was a strong and independent predictor for overall survival in 250 patients with 1-14 brain metastases treated with Gamma Knife surgery with a total tumor volume cutoff value of $\geq 2\, \text{cm}^3$ ($p = 0.008$) being a stronger predictor of overall survival than the number of brain metastases ($p = 0.098$) \textsuperscript{106}. Local tumor control at 1 year was 97% for lesions $< 2\, \text{cm}^3$ compared with 75% for lesions $\geq 2\, \text{cm}^3$ ($p < 0.001$). Median overall survival was 7.1 months and the 1-year local control rate was 91.5%. 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 ($p = 0.082$) \textsuperscript{106}.

**Brain Metastases from Breast Cancer**

Chemotherapy of breast cancer has made dramatic improvements over the last decade resulting in significantly prolonged patient survival, unfortunately without impact on brain metastases. A correspondingly effective treatment of brain metastases from breast cancer is paramount, but the standard fractionated whole brain radiotherapy is insufficient to allow a reliable control over brain metastases. The recently improved systemic therapeutic approaches for breast cancer patients emphasize the necessity for an equally effective radiosurgical treatment of the brain metastases.

**Local Tumor Control**

A Pubmed search provided a total of 9 clinical series after Gamma Knife radiosurgery radiosurgery treatment of breast cancer brain metastases with a total of 1137 published patients describing a local tumor control ranging between 71%-97% with a median local control of more than 85% in 5/9 studies in a total of 74% of all published patients (846/1137) \textsuperscript{98,107-114}.

Kondziolka, Lunsford and colleagues reported that sustained local tumor control was achieved in 90% of 350 consecutive female patients who underwent Gamma Knife radiosurgery for 1535 brain metastases patients. Symptomatic adverse radiation effects occurred in 6% of patients. Factors associated with longer progression-free survival included a better RPA class, fewer brain metastases, a smaller total tumor volume per patient, and a higher tumor margin dose \textsuperscript{112}. Another study after Gamma Knife surgery for brain metastases in 101 patients reported local tumor control
of 97%, and a tumor response rate of 82.3%\textsuperscript{111}. In a cohort of 62 patients with brain metastases from breast cancer treated by Gamma Knife surgery actuarial local control rate was 89.5±4.5% and 70.5±6.9% at 6 and 12 months after GKS, respectively. No prognostic factors were found to affect local control rate. Median survival after Gamma Knife was 73.0 weeks\textsuperscript{109}. A treated tumor volume >5000 mm\textsuperscript{3} was significantly correlated with poor local tumor control according to a multivariate analysis (hazard risk=7.091, p=0.01)\textsuperscript{107}.

The median survival time after Gamma Knife surgery was 16.0 months for 95 newly diagnosed patients brain metastases from breast cancer and 11.7 months for 81 patients with recurrent brain metastases\textsuperscript{113}.

**Tumor subtypes**

After analysis of a large multi-institutional retrospective database of 865 patients, Sperduto and colleagues concluded that tumor subtypes are an important prognostic factor for survival in patients with breast cancer. Patients with Basal (triple negative), HER2 (HER2 positive/ER/PR negative), Luminal B (triple positive) and Luminal A (ER/PR positive/HER2 negative) tumor subtypes had a median survival from primary diagnosis of 39.6, 66.4, 90.3 and 72.7 months (p < 0.01) and median survival from diagnosis of brain metastases of 7.3, 17.9, 22.9 and 10.0 months (p < 0.01), respectively. Patients with Basal and HER2 tumor subtypes have short time interval from primary diagnosis to development of brain metastases\textsuperscript{115}. The incidence of brain metastasis in patients with metastatic breast cancer ranges from 14 to 16%. Patients classified as triple-negative presented more frequently with brain metastasis as the first site (26%) than patients in the human epidermal growth factor receptor 2 (HER2)-positive (6%) or luminal (12%) subtypes\textsuperscript{116}. The analysis by Sperduto, Mehta and associates of a multi-institutional retrospective database of 400 breast cancer patients treated for newly diagnosed brain metastases showed that significant prognostic factors were Karnofsky performance status, HER2, ER/PR status, and the interaction between ER/PR and HER2. Among HER2-negative patients, being ER/PR positive improved median survival time from 6.4 to 9.7 months, whereas in HER2-positive patients, being ER/PR positive improved median survival time from 17.9 to 20.7 months\textsuperscript{117}.

In 154 breast cancer patients who had been treated with Gamma Knife surgery for brain metastases, multivariate analysis revealed that HER2+ status independently predicted improved survival (p =
0.007), while women with basal subtype had high rates of distant brain failure and worsened survival. **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) \(^{118}\). Survival benefit was associated with non-triple-negative phenotype status and lower recursive partitioning analysis class at the initial SRS in 103 breast cancer patients with brain metastases (multivariate analysis) \(^{119}\).

Advances in chemotherapy for breast cancer have prolonged overall survival, especially for patients with human epidermal growth factor receptor-2 (HER2) positive cancer. Patients with HER2-overexpressing tumors were found to be a distinct subgroup for which a longer survival time. In 80 consecutive patients who underwent Gamma Knife radiosurgery, the median survival time in HER2-positive and -negative patients were 16.6 and 7.1 months, respectively (P = 0.001) Survival benefit was associated with non-triple-negative phenotype status and lower recursive partitioning analysis class at the initial SRS in 103 breast cancer patients with brain metastases (multivariate analysis) \(^{120}\) and similarly (in 2014) median overall survival was 22 months for the HER2-positive group compared with 12 months for the HER2-negative group (p = 0.053) in another series of radiosurgically treated breast cancer patients with brain metastases \(^{121}\).

In 40 patients with HER2-overexpression, treatment results were compared between two subgroups: lapatinib-based therapy (24 patients) versus non-lapatinib-based therapy (16 patients). The rates of 1- and 2-year overall survival after gamma knife SRS were 50 and 26 %, respectively. Interestingly, in sub-analysis of patients with HER2-overexpression, lapatinib-based chemotherapy was also associated with better local tumor control (86% vs. 69 %, P < 0.001) \(^{120}\).

**Brain Metastases from Lung Cancer**

Patients with a complete response after multimodality therapy for locally advanced non-small cell lung cancer (NSCLC) are at high risk for the subsequent development of brain metastases. Chen found that 55% developed brain metastases. The 5-year estimates of brain metastasis-free survival for patients with squamous and non-squamous cancers were 57% and 34%, respectively \(^{122}\).
Local Tumor Control

A total of 18 clinical series after Gamma Knife radiosurgery treatment of NSCLC brain metastases with a total of 2660 published patients (10 series published after 2007) describing a local tumor control ranging between 74%-98% with a median local control of > 85% in 13/18 studies comprising 82% of published patients (2183/2660)\textsuperscript{123,74,124-136}.

Tumor subtypes

Histological subtype of lung cancer appears to predict outcomes. Multivariate analysis confirmed small cell carcinoma histology as a significant predictor of worsened local control (hazard ratio [HR]: 6.46, P = .025) and distant failure (HR: 3.32, P = .0027) in 271 patients with brain metastases from primary lung cancer treated with Gamma Knife surgery. For NSCLC histologies, squamous cell carcinoma predicted for worsened overall survival (HR: 1.77, P < .0121)\textsuperscript{137}.

EGFR tyrosine kinase mutation and ALK translocation results in improved response to targeted therapies but that mutation status itself does not predict survival and local control in patients with brain metastases from NSCLC: In 89 262 NSCLC patients treated with gamma knife radiosurgery for brain metastases genotyping was available: This cohort was selected to determine outcome predictors. Median overall survival 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). **Targeted therapy was a strong predictor of increased overall survival on univariate (P = .037) and multivariate (P = .022) analysis. Overall survival for targeted versus non-targeted therapy was 21 and 11 months, respectively (P = .071)**\textsuperscript{138}.

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 EGFR-mutant cases were re-categorized based on whether they received tyrosine kinase inhibitor, overall survival was no longer significantly shorter (hazard ratio: 1.5; P = .471). **Local failure rates were not different between tumor subtypes**\textsuperscript{138}.

Non-small cell lung cancer includes a spectrum of radiosensitive and radioresistant tumors. Others found that **EGFR mutation, ALK translocation, and metastasis size were independent predictors**...
for superior local control after gamma knife treatment, since 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)\textsuperscript{139}.

SCLC
The standard treatment of small cell lung cancer (SCLC) is fractionated whole brain radiotherapy, but WBRT does not protect from recurrences or new metastases. This situation is particularly difficult since WBRT cannot be repeated and patients generally have to remain untreated. Gamma Knife surgery appears to be as effective in treating brain metastases from SCLC as for those from NSCLC.

In a larger series of 245 patients with radiosurgically (Gamma Knife) treated brain metastases from lung cancer Serizawa et al. found that there was no significant difference in survival between patients with SCLC or NSCLC; this finding was verified by multivariate analysis \textsuperscript{130}. In a salvage situation Gamma Knife stereotactic radiosurgery has been successfully applied for new metastases in 51 patients with SCLC and previous WBRT. In this difficult clinical situation the 1-year local control rate was 57% with concurrent chemotherapy improving local control (HR = 89; p = 0.006) \textsuperscript{61}. This local control rate is comparatively low and at a higher median prescribed dose of 20.0 Gy, others found a tumor control rate of 95.8 % at a rather short median follow-up period of 4 months in 44 patients who were treated with Gamma Knife for recurrent or new SCLC-associated brain metastases after WBRT \textsuperscript{60}.

Another series reported a 1-year actuarial local control of 86% after Gamma Knife treatment of brain metastases from small-cell lung cancer. The overall survival was 9 months after Gamma Knife and new brain metastases outside of the treated area developed in 61% of patients at a median time of 7 months; 81% of these patients had received previous WBRT \textsuperscript{134}.

Local Control and Survival in Brain Metastases from NSCLC
In 2015 Bowden, Lunsford and associates reviewed 720 patients with NSCLC brain metastasis who
underwent Gamma Knife radiosurgery. The overall local tumor control rate in the entire group was 92.8%. 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. Post-radiosurgery survival was decreased in patients treated with prior whole-brain radiation therapy compared with SRS alone (p = 0.003). A total of 24% underwent repeat SRS for new or resistant metastatic deposits. In patients with NSCLC (n=373), who had undergone Gamma Knife radiosurgery for eight or fewer brain metastases, Motta and colleagues reported a mean overall survival of 14.2 months. The prescription dose was relative high (22.5 Gy). RPA class and overall tumor volume >5 cc were the only two covariates independently predictive of overall survival in patients who died of cerebral progression.

Previously Sheehan had published a retrospective review of 273 patients who had undergone Gamma Knife surgery (GKS) to treat a total of 627 NSCLC metastases. The overall median patient survival time was 10 months from GKS treatment in those patients with adenocarcinoma and 7 months for those with other histological tumor types. In patients with no active extracranial disease at the time of GKS, the median survival time was 16 months. Gamma knife surgery for NSCLC metastases offered effective local tumor control in approximately 84% of patients. In multivariate analyses, factors significantly affecting survival included: 1) female sex (p = 0.014); 2) preoperative Karnofsky Performance Scale score (p < 0.0001); 3) adenocarcinoma histological subtype (p = 0.0028); 4) active systemic disease (p = 0.0001); and 5) time from lung cancer diagnosis to the development of brain metastasis (p = 0.0074). Prior tumor resection or whole-brain radiation therapy did not correlate with extended patient survival time.

Serizawa showed in 245 patients with brain metastases from lung cancer a 1-year tumor control rate of 94.5% in the SCLC group and 98% in the NSCLC group. The median survival time was 9.1 months in the SCLC group and 8.6 months in the NSCLC group. The 1-year survival rates in the SCLC group were 86.5% for neurological survival and 68.9% for qualitative survival; those in the NSCLC group were 87.9% for neurological and 78.9% for qualitative survival. Similarly, 100 patients underwent Gamma knife radiosurgery treatment for 184 brain metastases from NSCLC at the Marmara University Hospital, Istanbul, Turkey and local tumor control was achieved in 95% of the metastases. In multivariate analysis, adenocarcinoma histology, Karnofsky performance status (KPS)
score > 80, 1-3 metastases and tumor diameter <2 cm were related to longer survival. Addition of WBRT did not have any effect on overall survival. A study of 42 patients with synchronous, solitary brain metastasis from NSCLC with a median KPS of 90 who were treated with Gamma Knife radiosurgery showed a rather positive prognosis with a median overall survival of 18 months and a 1-year actuarial OS rates of 71.3%. For patients who underwent definitive thoracic therapy, the median OS was 26.4 months compared with 13.1 months for those who had non-definitive therapy, and the 5-year actuarial OS was 34.6% vs. 0% (p < 0.0001). The prognostic factors significant on multivariate analysis were definitive thoracic therapy (p = 0.020) and KPS (p = 0.001). The 5-year OS of 21% demonstrates the potential for long-term survival in patients treated with gamma knife stereotactic radiosurgery. The authors argued that patients with good KPS should be considered for definitive thoracic therapy.

The overall survival was 70.8% at 1 year and the actuarial local control rate was 91.5% at 1 year and 85.5% at 2 years in 89 patients who underwent Gamma Knife SRS for 1-4 metastases, at Lille University Hospital (KPS score of 60 or greater; mean radiation dose 23.41 Gy; range 18-26Gy; mean tumor volume 2.47cm³; range 0.3-6.7cm³). The overall complication rate was 10.1%.

In 228 patients with non-small cell lung cancer treated with Gamma Knife radiosurgery (median prescription dose 20 Gy; range, 14-24 Gy), median overall survival from time of SRS was 12.1 months and estimated local control at 12 months was 74%. The adjusted Kaplan-Meier 1-year local control for conformality index ≥ 1.75 was 84% versus 69% for conformality index <1.75.

In 26 patients with incidentally-identified NSCLC brain metastases (KPS 90-100) the median survival was 8.2 months from diagnosis of brain metastases.

A very small but one of the few studies that compared the effectiveness of Gamma Knife radiosurgery for the treatment of multiple brain metastases from lung cancer with that of fractionated whole brain radiation therapy (WBRT) (n= 33) found that the 1-year overall survival rates were 47.7% in the Gamma Knife radiosurgery group and 10.5% in the WBRT group. The overall survival time in the GKS group was significantly longer than in the WBRT group (p=0.04).
Additional Chemotherapy (Temozolomide and Erlotinib)

Because temozolomide (TMZ) and erlotinib (ETN) cross the blood-brain barrier and have documented activity in NSCLC, a phase 3 study was designed to test whether these drugs would improve the overall survival associated with WBRT + SRS. Sperduto, Mehta and associated showed in a randomized study with 126 NSCLC patients (n=126) harboring 1 to 3 brain metastases that the addition of TMZ or ETN to WBRT + SRS in NSCLC patients with 1 to 3 brain metastases did not improve survival and possibly had a deleterious effect 143.

Chemotherapy in NSCLC

In a Korean randomized controlled trial of 105 patients with one to four asymptomatic brain metastases of non-small-cell lung cancer, patients were randomly assigned to receive stereotactic radiosurgery followed by chemotherapy or upfront chemotherapy. 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. The median OS time was 14.6 months in the SRS group and 15.3 months for the upfront chemotherapy group (P = 0.418). 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. The survival rate in this study was unexpectedly high. When the study was designed in 2008, the OS rate of 35% at 1 year (6–7 months of the median OS) was anticipated while in the current study, the 1-year survival rate was 57% in the GKS group and 58% in the observation group, and may be attributed to the relatively homogenous study population with better prognostic factors such as high adenocarcinoma histology (80%) and activated EGFR mutation (30%) 144.

Brain Metastases from Renal Cancer

Brain metastases of renal cell carcinoma are considered radioresistant. While brain metastases of renal cell carcinoma are considered unresponsive to fractionated WBRT with a reported survival of only 3.0-4.4 months 145, Gamma Knife treatment provided consistent local control rates of 74% - 96% in 9 clinical series after Gamma Knife radiosurgery of renal cell cancer brain metastases with a total of 583 published patients describing a local tumor control ranging between 74% - 96% with a
median local control > 85% in 7/9 studies comprising a total of 78% of published patients (453/583)\textsuperscript{146-154}. For RPA classes I median survival was between 18 and 24 months\textsuperscript{149,155}.

The addition of WBRT does not prevent the development of new remote tumors in patients with renal cell cancer metastases\textsuperscript{99,146}.

In brain metastases from renal cell carcinoma treated with gamma knife radiosurgery from 158 consecutive patients, sustained local tumor control was achieved in 92% of patients. Symptomatic adverse radiation effects occurred in 7%. Fifty-seven patients had undergone prior WBRT. The overall survival after SRS was 38% at 12 months, with a median survival of 8.2 months. Factors associated with longer survival included younger age, longer interval between primary diagnosis and brain metastases, lower recursive partitioning analysis class, higher Karnofsky performance status, smaller number of brain metastases, and no prior WBRT\textsuperscript{154}.

**Brain Metastases from Malignant Melanoma: Local Control and Survival**

Based on the limited local tumor control rate after WBRT, brain metastases of malignant melanoma are considered radioresistant. This restriction does not apply to radiosurgery, since various series after Gamma Knife radiosurgery of malignant melanoma report reproducible local tumor control rates between 63-90% in a total of 13 clinical series after Gamma Knife radiosurgery radiosurgery treatment of otherwise radioresistant melanoma brain metastases with a total of 1316 published patients with a median local control of more than 85% in 6 out of 13 studies and 47\% of published patients (614/1316)\textsuperscript{75,147,151,156-165}. Gamma knife radiosurgery for malignant melanoma brain metastases is safe and effective and provides a high rate of durable local control.

Mathieu and colleagues had reviewed 245 patients with malignant melanoma brain metastases treated with Gamma knife radiosurgery. The median tumor volume was 4.4 cm\(^3\). The median margin doses were 18 Gy. Sustained local control was achieved in 86.2\% of tumors and median survival was 5.3 months after radiosurgery. Patients survived a median of 7.8 months from the diagnosis of brain metastases and 44.9 months after the diagnosis of the primary tumor. Symptomatic radiation changes occurred in 6.6\%\textsuperscript{159}. Gamma-Knife radiosurgery without whole-brain radiotherapy was used in the management of 106 patients with brain metastases of malignant melanoma with a local control rate of 83.7\% at a median survival from the time of GKR of 5.09 months\textsuperscript{158}. Virtually identical results were achieved in 2014, when a total of 129 consecutive
patients were summarized after Gamma Knife radiosurgery for brain metastases from melanoma. The median survival time was 6.7 months. Local tumor control was 81% at 12 months. 166.

In 2011 Liew, Lunsford and colleagues reviewed 333 consecutive patients with melanoma who underwent SRS for 1570 brain metastases from cutaneous and mucosal/acral melanoma. Sustained local tumor control was achieved in 73% of the patients and actuarial survival rates were 25% at 12 months. There were 6% asymptomatic and 7% symptomatic radiation effects. Patients with ≤ 8 brain metastases, no prior WBRT, and the recursive partitioning analysis Class I had extended survivals (median 54.3 months) 156. In 77 patients who had been treated with Gamma knife radiosurgery for brain melanoma metastases, growth control was achieved in 89.1% of the tumors. The median survival was 7 months (range 0-73 months) after GKS and 67 months (range 4-327 months) from the time of diagnosis. A total tumor volume of less than 5 cc was associated with longer survival (P = 0.041). Survival was significantly longer in recursive partitioning analysis in RPA class 1 (22 months) than RPA class 2 (7 months) and RPA class 3 (3 months; P = 0.008) 75.

Powell and colleagues had previously reviewed the records of 50 patients with melanoma, who had undergone Gamma Knife treatment. The actuarial 12-month rate for freedom from local progression for melanoma was 63.0%. The percentage of coverage of the prescribed dose to target volume was the only treatment-related variable associated with local control: 12-month actuarial rate of freedom from local progression was 71.4% for lesions receiving ≥ 90% coverage versus 0.0% for lesions receiving < 90% (p = 0.00048) 147.

Chemotherapy

The survival of patients with melanoma brain metastases managed with ipilimumab and definitive radiosurgery can exceed the commonly anticipated 4-6 months. Using ipilimumab in a supportive treatment paradigm of radiosurgery for brain oligometastases was associated with an increased median survival from 4.9 to 21.3 months, with a 2-year survival rate of 19.7% versus 47.2% 167. Another study demonstrated in 2015 that survival of patients with melanoma brain metastases treated with ipilimumab combined with SRS may be comparable to patients without brain metastases with median survivals of 29.3 months from date of stage IV for melanoma brain metastases treated with ipilimumab and 33.1 months for patients without brain metastases,
respectively (HR = 0.93, \( P = 0.896 \)) \(^{168}\). In another retrospective study, administration of ipilimumab did not improve intracerebral disease control or survival in patients with limited brain metastases who received Gamma Knife SRS. The 6-month OS was 56\% in patients who received ipilimumab and 45\% in those who received SRS alone (\( P =0.18 \)) \(^{169}\).

A small study suggested that melanoma patients with brain metastases harboring BRAF mutation appear to be a distinct sub-group with a favorable response to vemurafenib and radiation therapy and acceptable morbidity \(^{170}\). While interrupting BRAF inhibitors treatment for melanoma patients is for still advised for other radiation therapies, interruption does not appear necessary in combination with stereotactic radiosurgery. Among 53 GKRS carried out in 30 patients who ever received BRAF inhibitors and Gamma-Knife radiosurgery, 33 Gamma-Knife radiosurgery were carried out in 24 patients while under BRAF inhibitors treatment, and no increased side effects were observed \(^{171}\).

**Brain Metastases from Colo-rectal Carcinoma**

A total of 6 clinical series after Gamma Knife radiosurgery treatment of colorectal cancer brain metastases with a total of 373 published patients describing a local tumor control ranging between 71\% - 96\% with a median local control > 85\% in 3/6 studies comprising 61\% of published patients (227/373) \(^{172-177}\). The addition of WBRT to radiosurgery did not improve survival and local tumor control rates \(^{176,177}\).

There are few reports on the effect of Gamma Knife surgery for brain metastases from colorectal cancer. Skeie, Pedersen and colleagues from the Haukeland University Hospital, Bergen, Norway studied 80 patients with 140 metastases with mean tumor volume of 6.13 cm\(^3\) (0.01-35.5); the prescription dose was 21.1 Gy. Growth control was achieved in 76.9\% and 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\%). The median survival was 6 months (range 0-75) after GKS. Radiation-induced edema was seen in 22.1\%, but was asymptomatic in 93.8\% \(^{178}\).

Matsunaga, Fujino and associates analyzed the outcomes in 152 patients with 616 brain metastases from colorectal cancer who had been treated with Gamma Knife at a mean prescription dose of 18.5 Gy (mean tumor volume 2.0 cm\(^3\)). The local tumor growth control rate was 91.2\%. The significant factors for unfavorable local tumor growth control, based on multivariate analysis, were larger
tumor volume ($p = 0.001$) and lower margin dose ($p = 0.016$). The median overall survival time was 6 months. The cause of death was systemic disease in 112 patients and neurological disease in 13 patients. A virtually identical tumor control rate was seen by others: Da Silva, Sheehan and colleagues from the University of Virginia, Charlottesville performed a retrospective review of 40 patients who had undergone Gamma Knife treatment for a total of 118 metastases from gastrointestinal cancers demonstrating a tumor control rate of 91% and a median survival time of 6.7 months.

In a rare comparison of outcome between Gamma Knife and fractionated whole brain radiotherapy, Park and colleagues reviewed 56 patients with brain metastases from advanced gastric cancer, treated with GKR or WBRT to assess prognostic factors affecting survival. Fifteen patients with brain metastases from advanced gastric cancer were treated with Gamma Knife and the median survival after treatment was 40.0 weeks [95% confidence interval (CI) 44.9-132.1 weeks] and median survival after WBRT was 9.0 weeks. The use of Gamma Knife was correlated with prolonged survival in univariate and multivariate analyses.

**Meningiomas**

Meningiomas are considered a classical indication for open microsurgery, but the surgical resection has to be complete to avoid local tumor recurrences. Microsurgery has been developed considerably within the recent decade but reaches its natural limitations in many anatomical locations in the brain. In frequent situations a complete resection of a meningioma is still difficult to achieve without significant side effects. Complete surgical removal of meningiomas in functional anatomical locations can be associated with a significant risk for postoperative neurological deficits. Consequently, the close involvement of eloquent or sensitive structures makes complete tumor resections virtually impossible when the neurological function is supposed to be preserved. Critical
anatomical regions are skull base, particularly the cavernous sinus and the petroclival region, but even complete resections of parafalcine meningioma can be complicated when the sagittal sinus is infiltrated.

Hence, when relevant and sensible structure are involved, the meningioma is often resected incompletely in order to preserve neurological function, but long term follow up studies have demonstrated that incompletely resected meningiomas carry a significant risk for symptomatic recurrences. Stereotactic radiosurgery has gained an important role in these situations and also in cases of smaller meningioma, which do not necessitate a surgical resection. Microsurgery can be completed or even replaced by Gamma Knife radiosurgery, which has changed the therapeutic spectrum in a significant way.

Treatment Doses
The necessary radiation doses to achieve tumor control are an important issue. While the majority of Gamma Knife centers apply doses of 15-16Gy to the tumor margin, Iwai studied 108 patients with benign cranial base meningiomas after low-dose Gamma Knife radiosurgery at a median prescription dose of 12 Gy (median tumor volume 8.1 cm$^3$). After a mean follow-up of 86.1 months the actuarial progression-free survival rate, including malignant transformation and outside recurrence, was 93% at 5 years and 83% at 10 years and permanent radiation injury occurred in 6% 181. On the other hand, a recent multicenter study of 763 patients with benign sellar and parasellar meningiomas showed that a tumor margin dose < 13 Gy significantly increased the likelihood of tumor progression after Gamma Knife treatment 182.

Tumor Control in Meningiomas in General

Few data are available concerning the natural history of meningiomas and the necessity to treat postoperative remnants has sometimes been questioned, but it has been shown that benign meningiomas grow slowly at highly variable growth rates with median doubling times ranging between 415 days and 8 years 183,184.

For the evaluation of the natural history of petroclival meningiomas, Van Havenbergh, Samii and colleagueus followed patients at a median of 85 months with regular clinical and radiological
monitoring. After a median follow-up of 85 months (range 48 to 120 months), radiological tumor growth was observed in 76% of the cases with associated functional deterioration in 63% of the growing tumors.

As a result, recent years have seen an essential modification in clinical neurosurgical approaches of meningioma, a shift away from aggressive surgical solutions toward a disease management with lower invasiveness. The current priority emphasizes the patient’s quality of life and avoidance of postoperative defects. Gamma Knife treatment allows a less aggressive upfront surgical approach with lower morbidity and lower complication rates. The aim of Gamma Knife treatments of meningioma is to achieve a growth arrest, in other words: local tumor control. The Gamma Knife treatment however, has a clear limitation in the tumor volume. In larger tumors the neurosurgical tumor removal is essential, but the more “sensible” parts of the tumor can be left in place and later be treated with the Gamma knife.

In summary Gamma Knife radiosurgery allows less aggressive or minimal invasive tumor resections and helps to reduce treatment induced side effects. Most large series after Gamma Knife radiosurgery demonstrate 5 year-actuarial tumor control rates for patients with grade I meningiomas in excess of 90%.

The 5-year-actuarial tumor control after Gamma Knife treatment of meningioma was reported as ranging between 91% and 99% of patients in 13 published Gamma Knife studies comprising 6268 meningioma patients.

Under the auspices of the European Gamma Knife Society (EGKS) a retrospective observational analysis of Gamma Knife radiosurgery for meningioma was carried out at 15 participating centers comprising 4565 consecutive patients harboring 5300 benign meningiomas. Detailed results from 3768 meningiomas were analyzed and published. The 5- and 10-year progression-free survival rates were 95.2% and 88.6%, respectively. Tumor control was higher for imaging defined tumors vs grade I meningiomas (P < .001), for female vs male patients (P < .001), for sporadic vs multiple meningiomas (P < .001), and for skull base vs convexity tumors (P < .001). Permanent morbidity rate was 6.6% at the last follow-up.

Similarly, Kondziolka, Flickinger and colleagues had studied a cohort of 972 patients with 1045 intracranial meningiomas treated with Gamma Knife radiosurgery as definitive management during
an 18-year period. The overall control rate for patients with benign meningiomas (WHO Grade I) was 93%. For patients with WHO Grade II and III tumors, tumor control was 50 and 17%, respectively. Delayed resection after radiosurgery was necessary in only 5% at a mean of 35 months. After 10 years, Grade 1 tumors were still controlled in 91%. The overall morbidity rate was 7.7%. Symptomatic peritumoral imaging changes developed in 4% of the patients at a mean of 8 months.

Similar results with 5-year actuarial control rates of 87% for typical meningiomas, 49% for atypical tumors and 0% for malignant lesions has also been shown previously by Malik, Kemeny and colleagues in a systematic review of a consecutive series of 309 meningiomas treated with gamma knife stereotactic radiosurgery. Complications from radiosurgery were rare, occurring in 3% of tumors, and were most frequently trigeminal and eye movement disturbances treating cavernous sinus meningiomas.

Long-Term Outcome

In an attempt to determine whether long-term outcomes remain stable over time, Kondziolka, Lunsford and colleagues studied 290 consecutive patients who had undergone Gamma Knife radiosurgery for a meningioma (median tumor margin dose 15 Gy; median tumor volume 5.5 mL). The overall tumor control rate was 91%. And the 10- and 20-year actuarial rates of freedom from tumor progression of the targeted tumor were 87.7%±2.5% and 87.2%±4.2%. Of 234 patients who had symptoms before SRS, 26% improved, 54% had no change in symptoms and 20% gradually worsened. Adverse radiation effects were detected in 3.1% of patients.

In a retrospective review of 251 patients having SRS for imaging-defined intracranial meningiomas Pollock found a 3- and 10-year local control rate of 99.4% with 3.2% of patients having temporary and 9.2% permanent symptomatic radiation-related complications. Radiation-related complications were associated with convexity/falx tumors and increasing tumor volume.

Large Meningioma

Starke, Sheehan and associates reviewed 75 patients with tumors greater than 8 cm³ in volume,
which was defined as a large tumor. After a mean follow-up of 6.5 years (range 0.5-21 years), the tumor volume was unchanged or decreased in 84%. Actuarial rates of progression-free survival at 5 and 10 years were 88.6%, and 77.2%, respectively. In Cox multivariable analysis, covariates associated with tumor progression were history of radiotherapy (p=0.006), and tumor volume greater than 14 cm³ (p=0.066). Neurological function was deteriorated in 17%. Tumor progression was present in 64% of patients with new or worsening neurological decline.

<table>
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<tr>
<th>Actuarial tumor control rate at 5 year</th>
<th>Median follow-up</th>
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### Specific Anatomical Meningioma Locations

#### Cavernous Sinus and Skull Base Meningiomas

Starke and Sheehan and colleagues reviewed the outcomes in 255 patients with skull base meningiomas treated at the University of Virginia and found that actuarial progression-free survival at 5, and 10 years was 96%, and 79%, respectively. In Cox multivariate analysis, tumor progression included age greater than 65 years decreasing dose to tumor margin. At most recent clinical follow-up 10% of patients had deteriorated in their neurological condition. In multivariate analysis, the factors predictive of new or worsening symptoms were increasing duration of follow-up, tumor
progression, decreasing maximum dose, and petrous or clival location versus parasellar, petroclival, and cerebellopontine angle location

Pollock, Foote and colleagues studied 115 patients with cavernous sinus meningiomas with 5% showing tumor progression (in field, n = 3; marginal, n = 3) at a median of 74 months (range 42-145 months) after SRS. The local tumor control rate was 99% at 5 years and 93% at 10 years after SRS. Fourteen patients (12%) had permanent complications at a median onset of 23 months. The complication rate for patients with a treatment volume of 9.3 cm$^3$ or less was 3% compared with 21% for patients with a treatment volume greater than 9.4 cm$^3$.

Skeie analyzed 100 patients with meningiomas involving the cavernous sinus who had received Gamma Knife radiosurgery at Haukeland University Hospital, Bergen, Norway and who were followed for a mean of 82.0 months showing tumor growth control in 90.4% of benign meningiomas. The 5- and 10-year actuarial tumor growth control rates were 94.2%, and 91.6%, respectively. The complication rate was 6%. At last follow-up, 88.0% of patients were able to live independent lives.

Similarly, 98 patients with skull base meningiomas were treated with Gamma Knife radiosurgery at Teikyo University School of Medicine, Tokyo, Japan and were followed a median period of 53.2 months (12.2-204.4 mo), showing local tumor control rates were of 86.9% and 78.9% at 5 years and 10 years, respectively. Tumors with volume of 4 cm$^3$ or smaller (97.5% vs. 76.1% at 5 years, p = 0.001) and tumors completely included within the isodose line of 14 Gy or more (p = 0.0006) showed higher local control rates. Cranial nerve deficits deteriorated in 3%.

A series of 192 patients with skull base meningiomas treated with Gamma knife radiosurgery at the Na Homolce Hospital, Prague had been published in 2004. This series is interesting since contact with the chiasma or optic tract was present in 32% and was not regarded as a contraindication for gamma knife radiosurgery. Neurological deficit improved in 63% of patients, temporary morbidity occurred in 11% and persistent morbidity remained in 4.5%. The risk for the development of a radiation–induced edema was lower in patients with no history of edema prior to radiosurgery and in meningiomas of the posterior skull base and at prescription ≤ 14 Gy.
A series of 101 patients with skull-base meningiomas were treated with Gamma Knife at Nakamura Memorial Hospital, Sapporo, Hakkaido, Japan with a mean follow-up period of 51.9 months showing a tumor control rates of 95.5% in cavernous sinus meningiomas and 98.4% in posterior fossa and skull-base meningiomas \(^{207}\).

In a series of 63 patients with skull base meningiomas treated with Gamma Knife radiosurgery who had been followed for more than 48 months, the actuarial 5-year tumor control rate was 90.2% (mean tumor volume: 6.5 cm\(^3\): range 0.5-18.4 cm\(^3\), mean marginal dose :12.6 Gy: range, 7.0-20.0 Gy) \(^{208}\). Similarly a retrospective review of 136 patients with meningiomas who received gamma knife radiosurgery progression-free survival rates at 5, and 10 years were 95% and 85%, respectively \(^{209}\).

**Sellar and Parasellar Meningiomas**

Due to their involvement of neurovascular and endocrine structures, complete resection of parasellar and sellar meningiomas can be associated with significant morbidity, and incomplete resections are common. At 10 centers a multicenter study of patients with benign sellar and parasellar meningiomas was conducted through the North American Gamma Knife Consortium. and 763 patients were identified with 50.7% having undergone at least one resection before Gamma Knife. The median follow-up after GKRS was 66.7 months (range 6-216 months). At the last follow-up, tumor volumes remained stable or decreased in 90.2% of patients and actuarial progression-free survival rates at 5 and 8 years were 95% and 88%, respectively. A tumor margin dose < 13 Gy significantly increased the likelihood of tumor progression after GKRS. At the last clinical follow-up, 13.8% of patients had experienced symptom progression \(^{182}\).

The group University of Virginia, Charlottesville had separately analyzed the outcomes of Gamma Knife surgery used in 138 patients with parasellar meningiomas at a median follow-up duration 75.5 months (range 24-216 months) and showed that in 86% the tumor volume was unchanged or had decreased at last follow-up while 10% developed new cranial nerve palsies. Kaplan-Meier analysis demonstrated radiographic progression-free survival at 5 and 10 years to be 95.4% and 69%, respectively \(^{210}\).
Petroclival Meningiomas
A multicenter study of 254 patients with a benign petroclival meningioma was conducted through the North American Gamma Knife Consortium. One hundred and forty patients were treated with upfront radiosurgery, and 114 following surgery. At mean follow up of 71 months (range 6-252), tumor volumes increased in 9 % of tumors, remained stable in 52 %, and decreased in 39 %. Kaplan-Meier actuarial progression free survival rates at 10 years were 84 %. At last clinical follow-up, 93.6 % of patients demonstrated no change or improvement in their neurological condition whereas 6.4 % of patients experienced progression of symptoms.

Petroclival meningiomas were treated with Gamma Knife radiosurgery in 168 patients and analyzed by Flannery, Kondziolka and colleagues after a median follow-up of 72 months (median tumor volume: 6.1 cm³; range 0.3-32.5 cm³, median prescription dose: 13 Gy;range 9-18 Gy) showing overall 5- and 10-year progression-free survival rates of 91 and 86%, respectively. Significant risk factors for tumor progression were a tumor volume > or = 8 cm³ (p = 0.001) and male sex (p = 0.02).

Convexity Meningiomas
The same group also analyzed 125 patients with convexity meningiomas managed using Gamma Knife radiosurgery. For patients with benign tumors (Grade I) and those without prior surgery, the actuarial tumor control rate was 95.3±/-2.3% and 85.8±/-9.3%, respectively. The overall morbidity rate was 9.6%. Symptomatic peritumoral imaging changes compatible with edema or adverse radiation effects developed in 5%, at a mean of 8 months.

Posterior Fossa Meningioma
At 7 medical centers participating in the North American Gamma Knife Consortium, 675 patients undergoing SRS for a posterior fossa meningioma were identified (mean tumor volume 6.5 cm³, median margin dose of 13.6 Gy; range 8-40 Gy). At a mean follow-up of 60.1 months, tumor control was achieved in 91.2% of cases. Actuarial tumor control was 81% at 10 years after radiosurgery. Patients with a smaller tumor volume and no prior radiation therapy were more likely to have a favorable response after radiosurgery.

Tentorial Meningioma
Thirty-nine patients with tentorial meningiomas underwent SRS using various Gamma Knife technologies (median tumor volume 4.6 cm$^3$; range 0.5-36.6 cm$^3$; median prescription dose 14 Gy; range 8.9-18 Gy). The median follow-up period was 41 months (range 6-183 months). At the last imaging follow-up, tumor volumes decreased in 22 patients (57%), remained stable in 13 patients (33%), and increased in 4 patients (10%). At the last clinical follow-up, 8% demonstrated worsening symptoms.

Cerebellopontine Angle Meningiomas

From 7 institutions participating in the North American Gamma Knife Consortium, 177 patients with benign cerebellopontine angle meningiomas treated with GKRS were included for analysis (median tumor volume 3.6 cc; median prescription dose 13 Gy). The mean radiologic follow-up was 47 months. The actuarial rates of progression-free survival at 5 and 10 years were 93% and 77%, respectively. Male sex ($P = .014$), prior fractionated radiation therapy ($P = .010$) were independent predictors of tumor progression. Symptomatic adverse radiation effects and permanent neurological deterioration were observed in 1.1% and 9% of patients, respectively.

Olfactory Groove Meningioma

In the treatment of olfactory groove meningioma stereotactic radiosurgery provided both long-term tumor control and preservation of olfaction.

Gamma Knife stereotactic radiosurgery of olfactory groove meningioma was studied in 41 patients with median clinical and imaging follow-up of 76 and 65 months, respectively (median tumor volume 8.5 cm$^3$; range 0.6-56.1; mean prescription dose 13 Gy; range 10-20; median estimated dose to the olfactory nerve was 5.1 Gy; range 1.1-18.1). No patient reported deterioration in olfaction after radiosurgery. The progression-free tumor control rates were 95% at 2, 10 and 20 years. Symptomatic adverse radiation effects occurred 7%.

Parasagittal and Parafalcine Meningiomas

Hasegawa studied 46 patients harbouring convexity, parasagittal, or falcine meningiomas undergoing Gamma Knife radiosurgery (median tumor volume: 8 cm$^3$, median prescription doses: 16 Gy) with actuarial 5- and 10-year local tumor control rates of 87% and 71%, respectively. The actuarial symptomatic radiation-induced edema rate was 7%. Out of 6 patients with pre-
radiosurgical edema, 4 developed severe panhemispheric edema after GKS. The authors concluded that radiation-induced edema is more common in convexity, parasagittal, and falcine meningiomas than skull base meningiomas.218

A virtually identical outcome was reported by Ding, Sheehan and associates who retrospectively reviewed 65 patients with 90 WHO Grade I parasagittal (59%) and parafalcine (41%) meningiomas after a mean MRI follow-up of 56.6 months (median treatment volumes 3.7 cm³, median prescription dose 15 Gy). The actuarial tumor control rate was 85% at 3 years and 70% at 5 years. Symptomatic postradiosurgery peritumoral edema was observed in 8.2%. Two patients (4.1%) died of tumor progression.219

Zada, Apuzzo and colleagues reviewed in 116 patients who underwent Gamma Knife treatments for benign intracranial meningiomas (n=116; median tumor volume: 3.4 cm³, median prescription dose:16 Gy) finding overall tumor control in 94% and an overall 5-year and 10-year actuarial tumor control rate of 98.9% and 84% with complications appearing in 8%, generally in larger meningiomas (11 vs 5.7 cm³, P = .003). Tumor progression occurred at a mean time of 7.5 years after GKRS, reinforcing the need for long-term surveillance despite initial tumor control. Treatment failure was related to undercoverage of lesions in the majority of cases, with the remainder demonstrating evidence of abnormal tumor biology.220

Combination Surgery/Radiosurgery

Meningiomas with growth onto or into the major venous sinuses, that is, venous meningiomas, provide management problems regarding their radical removal and preservation of venous drainage. The relationship to venous structures often precludes radical surgery; the risk of recurrence and aggressive histology is greater for parasagittal meningiomas than in other locations.

The surgical approach to inresectable tumor remnants would be a ‘wait-and-see’ attitude with a potential removal only if the regrowing tumor has reached a local clinically relevant mass effect. Gamma Knife radiosurgery of remnant tumors is an alternative option. Treatment, histopathology,
and follow-up data of 100 consecutive patients undergoing surgery for venous meningiomas were prospectively collected by Mathiesen, Ulfarsson and colleagues at the Karolinska Hospital, Stockholm. Patients with Simpson grade 1 surgery had a recurrence rate of 10%. Gamma-knife surgery was considered as a direct postsurgical adjunct or as an adjunct after a period of radiological follow-up. Patients with deliberate nonradical surgery (Simpson grade IV) had a tumor recurrence rate of 72%, whereas a combined treatment of direct gamma-knife radiosurgery after a tailored microsurgical resection (Simpson IV gamma) allowed return to a low recurrence rate of 10% 221.

**Malignant and Atypical Meningioma**

Atypical or malignant meningiomas are associated with high levels of recurrence and mortality and a significantly higher local recurrence rate is reported after radiosurgery of these aggressive meningiomas.

Out of 228 patients with microsurgically treated atypical meningiomas at the Barrow Neurological Institute, gross total resections were achieved in 58%. Overall 22% demonstrated tumor recurrence at a median of 20.2 months postoperatively. The recurrence rate for patients receiving SRS was 25% and for IMRT was 18% 222.

Even after stereotactic radiosurgery atypical or malignant meningiomas have a high risk for local recurrence: Tumor recurrence after Gamma Knife radiosurgery was identified in 31.4% of patients with atypical and malignant meningiomas (n=35). Three-year overall survival and progression-free survival rates were 78.0% and 65.0%, respectively. WHO grade II 3-year OS and progression-free survival were 83.4% and 70.1%, respectively, while WHO grade III 3-year OS and progression-free survival were 33.3% and 0%. Larger tumor size predicted poor survival, while nuclear atypia, necrosis, and increased mitotic rate are risk factors for recurrence 223.

Similarly, another series with atypical meningiomas (n=9) and anaplastic meningiomas (n=7) (mean tumor volume 7.1 cm³; mean marginal doses 18.8 Gy; mean length of follow-up 37.1 months) showed stabilization of tumor growth during after Gamma Knife radiosurgery in 29%, which was significantly associated with small tumor volume, and greater marginal irradiation doses. In this series 31 % died because of tumor progression within the average time period of 16.8 months after treatment 224.
A virtually identical tumor control of 34% at 3 years was seen in another series of 30 patients with (WHO) grade II or grade III meningiomas who had undergone Gamma Knife surgery in Pittsburgh, or in 22 patients with atypical meningioma who underwent Gamma Knife at the University of Tokyo Hospital with local control rates of 39%, and 16% at 2 and 5 years, respectively. Hanakita, Saito, and colleagues stated that a margin dose higher than 18 Gy (p = 0.02), and a Karnofsky Performance Scale (KPS) score of 90 or more (p = 0.02) were factors associated with a longer duration of tumor control in the univariate analysis.

Using a multivariate analysis, Kim, Jung, and colleagues found that the mitotic count (≤8 per 10 high-power fields; HPF) and the MIB-1 proliferation marker labeling index (LI; ≤8%) were significant favorable prognostic factors for the radiosurgical outcomes of patients with non-benign meningiomas. The actuarial local tumor control rates for 35 patients with atypical meningiomas at 2 and 3 years after radiosurgery were 53 and 36%, respectively, whereas those for anaplastic meningiomas were 35% at 1 year and 10% at 2 years.

**Acoustic Neuroma**

Acoustic Neuromas (vestibular schwannomas) are generally slow-growing, intracranial extra-axial benign tumors that usually develop from the vestibular portion of the eighth nerve. A progressive unilateral hearing decline is the most common symptom that leads to the diagnosis of a vestibular schwannoma. Vestibular schwannomas (Acoustic Neuroma) are accounting for approximately 10% of newly diagnosed intracranial tumors occurring at a frequency of 2000 to 2500 new cases per year in the United States. Acoustic Neuroma is a benign tumor with anatomically close association with the vestibular, the cochlear and the facial nerves. With increasing volume acoustic neuromas can exert pressure on the brainstem. The typical tumor location adjacent to the brainstem in connection with the close involvement of the described cranial nerves explains the need for tumor
control, but also the problems that arise when these benign tumors are surgically removed, because generally after open tumor resection hearing cannot be preserved and even the facial nerve can be endangered by surgery.

As to therapeutic options for acoustic neuromas, the controversies have been fierce and not rarely polemic. Therapeutic options include microsurgical removal, radiosurgery, or possibly fractionated radiotherapy and even monitoring without treatment. Previously acoustic neuromas were the domain of surgery alone. Surgical resection however, is associated with a significant risk for side effects: loss of hearing, potential facial nerve damage and general morbidity.

A questionnaire concerning postoperative symptoms and the Short Form 36 (SF-36) QOL instrument was mailed to 97 consecutive patients who had undergone acoustic neuroma surgery via the translabyrinthine approach. The respondents’ QOL was rated significantly below published norms and their work capacity was reportedly reduced. The majority (63%) of respondents reported facial nerve dysfunction postoperatively. Balance problems were exacerbated by movement in 74% of patients, and 28% believed that their balance problem was incapacitating. Of those who had experienced recovery of facial nerve function, 63% reported that it had taken longer than 9 months. 32% of respondents reported a change in employment as a result of their acoustic neuroma.

Gamma Knife is highly effective in stopping potential tumor growth while preserving normal postoperative facial function and hearing with low treatment associated side effects. The goal of every acoustic neuroma management is to provide the best outcome with the lowest possible risk level. The long-term results after radiosurgical treatment are comparable and often even superior to the best results with open microsurgical techniques. Tumor control was achieved in 87-96% of 1179 published patients in 5 studies published between 2002 and 2005.

Myrseth and colleagues conducted a prospective, open, non-randomized study of treatment-associated morbidity in patients undergoing either microsurgery or Gamma Knife radiosurgery for vestibular schwannomas in 91 patients. None of the patients who underwent surgery had serviceable hearing postoperatively, while 68% patients preserved hearing after Gamma Knife treatment. Quality of life was significantly better in the Gamma Knife group at 2 years. The mean hospital stay was 2.5 days (range, 2–5 days) in the Gamma Knife group and 12.5 days (range, 10–30 days) in the surgery group (P< 0.0009, Student’s t test).
Conservative Management of Vestibular Schwannoma

Natural history and outcome was studied following the conservative management of 72 patients with unilateral vestibular schwannomas. The mean duration of follow-up was 80 months (range 52-242 months). Hearing deterioration with pure tone averages and speech discrimination scores occurred irrespective of tumor growth. The mean tumor growth rate for the entire group at the second review was 1 mm/year (range -0.84-9.65 mm/year). There was significant tumor growth seen in 38.9%, no or insignificant growth in 41.7% 236. In order to determine the outcomes and risks of conservative management of acoustic neuromas, gamma-knife radiosurgery, and microsurgery Yamakami, Yamaura and colleagues performed a systematic review and analyzed data from 903 patients with conservative management, 1475 with Gamma Knife radiosurgery, and 5005 with microsurgery from 38 studies identified in MEDLINE searches. Conservative management over a 3.1-year period resulted in tumor growth in 51% of acoustic neuromas with an average growth rate of 1.87 mm per year, and 20% of acoustic neuromas ultimately required surgical intervention. After conservative management a third of the patients lost useful hearing. Gamma Knife radiosurgery significantly reduced the percentage of acoustic neuromas that enlarged to 8%, and reduced the percentage that underwent microsurgery to 4.6% over a 3.8-year period. Microsurgery resulted in tumor recurrence in 1.8%, in mortality in 0.63%, and major disability in 2.9%, respectively 237.

Due to the invasiveness and associated morbidity of surgery and due to the certainty of postoperative hearing loss the traditional surgical policy in intracanalicular vestibular schwannoma has previously been to monitor the tumor and to treat only in case of significant growth or a significant mass effect. Regis and colleagues tested this ‘wait-and-see strategy’ in 47 patients versus a control group of 34 patients who had been treated with proactive Gamma Knife surgery in the treatment of small intracanalicular vestibular schwannomas in 47 patients and who were followed prospectively. In the wait-and-see group, there was tumor growth in 77%. At 3, 4, and 5 years, the useful hearing preservation rates were 75%, 52%, and 41% in the wait-and-see group and 77%, 70%, and 64% in the Gamma Knife control group, respectively. The authors concluded that the chances of maintaining functional hearing and avoiding further intervention were higher in cases treated by GKS (79% and 60% at 2 and 5 years, respectively) than in cases managed by the wait-and-see strategy (43% and 14% at 2 and 5 years, respectively). As a result, proactive Gamma Knife
radiosurgery was recommended at the time of diagnosis when hearing is still useful \(^{238}\).

Similarly Breivik, Lund-Johansen and associates showed that **Gamma Knife radiosurgery reduced the tumor growth rate and thereby the incidence rate of new treatment about tenfold.** Hence, the need for treatment following initial Gamma Knife or conservative management differed at highly significant levels (log-rank test, \(P < .001\)). Prospectively data of patients with unilateral vestibular schwannoma extending outside the internal acoustic canal had been collected and the outcome after Gamma Knife treatment (n=113) was compared with patients following conservative management (n=124). Mean follow-up time was 55.0 months. Serviceable hearing was lost in 76% after conservative management and in 64% after Gamma Knife. Hearing is lost at similar rates in both groups. Symptoms and quality of life seem not to be significantly affected by Gamma Knife \(^{239}\).

Patients with \(\leq 3\) cm vestibular schwannoma who underwent primary microsurgery, gamma knife surgery, or observation at 2 independent hospitals were identified and were surveyed via mail after a mean time of 7.7 years after initial treatment, and a total of 539 respondents were analyzed. More than 75% of all patients had nonserviceable hearing at the last clinical follow-up. Patients in the surgical series had the greatest hearing loss. In this series active treatment with microsurgery or Gamma Knife surgery did not appear to be protective, because patients who were observed had the greatest probability of durable hearing \(^{240}\).

**Tumor Control**

In 2004 Regis and colleagues had initially reviewed the outcome in the first 1000 patients with cerebello-pontine angle schwannomas that were consecutively treated by Gamma Knife at the LaTimone University Hospital, Marseille. Tumor control at last follow-up was 97%. Globally, a clinical trigeminal injury was observed in 0.6% of the patients and a facial palsy in 1.3%. There was clearly a decrease of the incidence of neuropathies with time; no facial palsy being reported among the last 258 patients. The rate of functional hearing preservation (Gardner) for patients initially in class I was 77.8% (47.6% for class II) at 3 Years. This rate of functional preservation reached 95% among patients with tinnitus as a first symptom \(^{233}\).
In another large retrospective analysis Lunsford, Kondziolka and colleagues analyzed the outcome after Gamma Knife treatment of vestibular schwannomas in 829 patients with VSs who had been treated between 1987 and 2002 at the University of Pittsburgh (average tumor volume 2.5 cm³; median prescription dose 13 Gy, range 10-20 Gy). **Tumor control rates without need for additional treatment at 10 years were 97%**. Unchanged hearing preservation was achieved in 50 to 77% of patients (up to 90% in those with intracanalicular tumors). Facial neuropathy risks were less than 1%. **Trigeminal symptoms were detected in less than 3% of patients whose tumors reached the level of the trigeminal nerve**. No patient sustained significant perioperative morbidity. The average duration of hospital stay was less than 1 day \(^{228}\).

Murphy, Suh and colleagues analyzed the long-term outcome of 117 patients with vestibular schwannoma who had been treated with Gamma Knife radiosurgery at the Cleveland Clinic (mean tumor volume 1.95 ± 2.42 ml; prescription dose 13 Gy in 82%, 13 Gy in 14%). **Imaging-documented tumor progression was present in 7.8%**, but in 3/8 of these the lesion eventually stabilized. Only 5 patients required a neurosurgical intervention. The estimated **1-, 3-, and 5-year rates of progression to surgery were 1, 4.6, and 8.9%**, respectively. One patient (1%) developed trigeminal neuropathy, 5% developed permanent facial neuropathy, 4% reported vertigo, and 18% had new gait imbalance following Gamma Knife treatment \(^{241}\).

The high local control rate was confirmed by Delbrouck, Massager and colleagues from the Erasmus Hospital of Brussels who demonstrated after Gamma Knife radiosurgery in 415 patients that unilateral vestibular schwannoma were stable or declining in size in 90.44% of cases. **At minimum one-year audiological follow-up, serviceable hearing was preserved in 65.97%** \(^{242}\).

Chung, Pan and colleagues performed a retrospective study of 195 patients with acoustic neuroma who had been treated with Gamma Knife radiosurgery (mean tumor volume 4.1 cm³; range 0.04-23.1 cm³; prescription dose: 11-18.2 Gy). **During a median follow-up period of 31 months resection was avoided in 96.8% of cases**. Twelve of 20 patients retained serviceable hearing. Two patients experienced a temporary facial palsy. Two patients developed a new trigeminal neuralgia. There was no treatment-related death \(^{231}\).

**Long-term Outcomes**
The recording of long-term outcomes is essential in the treatment of slowly growing benign tumors. Hasegawa, Yoshida and colleagues followed 73 patients harbouring acoustic neuromas over median of 135 months after Gamma Knife treatment (mean tumor volume 6.3 cm³, mean prescription doses 14.6 Gy). The actuarial 10-year progression-free survival rate was 87% overall, and 93% in patients with tumor volumes less than 10 cm³. No patient experienced malignant transformation.

Sun and Liu from the Beijing Neurosurgical Institute assessed the long-term clinical outcomes in 200 patients who underwent Gamma Knife surgery (median tumor margin dose 13.0 Gy; range 6.0-14.4 Gy; median tumor volume 3.6 cm³; range 0.3-27.3 cm³). After a median duration of follow-up of 109 months (range 8-195 months), the tumor control rate was 89.5%. Using the Kaplan-Meier method, the authors found the estimated 5-, 10-, and 15-year tumor control rates to be 93%, 86%, and 79%, respectively; and the estimated 3-, 5-, and 10-year hearing preservation rates were 96%, 92%, and 70%, respectively. For unknown reasons, the rate of side effects in this study was comparatively high, since 13.7% exhibited transient mild facial palsy or facial spasm was seen and 1.1% persistent mild facial palsy, while 2.6% suffered from persistent mild facial numbness.

Long-term data were reviewed from a consecutive cohort of 128 patients with vestibular schwannoma treated with Gamma knife radiosurgery at Karolinska University Hospital with a median follow-up time of 104 months (range 11-165) and radiological median follow-up of 86 months (range 5-170). Tumor control was achieved in 92% of patients after a single Gamma Knife treatment. Neither pre-treatment growth of the vestibular schwannoma, or a large tumor size (Koos grade 3 & 4) was correlated with a higher degree of treatment failure.

Quality of Life

The impact of Gamma Knife radiosurgery on the quality of life 97 of patients with a sporadic vestibular schwannoma was analyzed using the medical outcome study short form 36 (SF-36) and Glasgow benefit inventory (mean tumor size was 17 mm; range 6-39 mm; mean marginal dose 11.1 Gy; range 9.3-12.5 Gy). While there was a wide range in individual quality of life results, this study showed that GKRS for sporadic vestibular schwannoma has little impact on the general quality of
life of the vestibular schwannoma patient. A similar study monitored 59 patients with vestibular schwannoma after Gamma Knife treatment with a median follow-up of 15 months in a prospective follow-up algorithm including 36-item Short Form Health Survey (SF-36), Hearing Handicap Inventory, Dizziness Handicap Inventory, Tinnitus Handicap Inventory, pure-tone average, and speech discrimination hearing scores (Gardner-Robertson and American Academy of Otolaryngology), performed before and after Gamma Knife radiosurgery at 1-, 3-, 6-, 12-, and 18-month post-treatment intervals. Approximately 47% of patients with baseline serviceable hearing maintained serviceable hearing at 12 months. Although it can be criticized that the study had a relatively short follow-up and approximately 50% survey completion, it was demonstrated that no significant decline in global quality of life occurred after Gamma Knife radiosurgery.

Long-term data were reviewed from a consecutive cohort of 128 patients with vestibular schwannoma treated with Gamma knife radiosurgery. Median follow-up time was 104 months (range 11-165). Data on quality of life (EQ-5D score) were obtained in 90% of all cases at the end of follow-up, showing low morbidity and a high quality of life with median index of 0.91 (max. score 1.0).

Intracanalicular Acoustic Neurinoma

In general, patients with intracanalicular vestibular schwannoma have limited symptoms, while a surgical approach invariably causes a loss of hearing and other potential side effects. Hence the ‘surgical tradition’ in these tumors has been a wait-and-see strategy until a clinically relevant mass effect is reached. Since radiosurgery has a considerably lower risk profile, this policy has been questioned with regard to functional preservation. Regis, Roche and colleagues have followed 47 patients harboring an intracanalicular vestibular schwannomas prospectively over a mean period of 43.8 ± 40 months (range 9-222 months). And have compared this population with a control group of 34 patients harboring a unilateral intracanalicular vestibular schwannomas who were consecutively treated by Gamma Knife surgery and had functional hearing at the time of radiosurgery. In the wait-and-see group, there was tumor growth in 77% of the 47 patients in the
wait-and-see group, treatment failure (tumor growth requiring treatment) was observed in 74%, while treatment failure in the control Gamma Knife group occurred in only 3%. In the wait-and-see group 38% experienced more than 10 db of hearing loss and 2 of them became deaf. At 3, 4, and 5 years, the useful hearing preservation rates were 75%, 52%, and 41% in the wait-and-see group and 77%, 70%, and 64% in the Gamma Knife group, respectively.

The chances of maintaining functional hearing and avoiding further intervention were 60% at 5 years in cases treated by Gamma Knife and 14% at 5 years in cases managed by the wait-and-see strategy. The consequence is a policy change with a general recommendation of earlier Gamma Knife treatment even without relevant mass effect due to an improved chance of functional preservation.

Hearing Preservation

Many patients with acoustic neuromas have hearing function at diagnosis the current priority is to maintain it.

In 2009 Yang, Parsa and colleagues had performed a systematic analysis of the literature in English reviewing a total of 254 published studies reported assessable and quantifiable outcome data of patients undergoing radiosurgery for vestibular schwannomas. A total of 74 articles including 5825 patients met the inclusion criteria of reporting assessable and quantifiable outcome data of patients with preserved hearing with an average overall follow-up of 41.2 months. It was shown that practitioners who delivered an average prescription dose of 12.5 Gy reported having a higher hearing preservation rate (12.5 Gy=59% vs. >12.5 Gy=53%, p=0.0285). Age of the patient was not a significant prognostic factor for hearing preservation rates (<65 years=58% vs. >65 years=62%; p=0.4317). The average overall follow-up was 41.2 months. The data suggest that an overall hearing preservation rate of about 57% can be expected after radiosurgical treatment.

In a similar review from the same group published in 2010 it was shown that tumor volume was not
predictive for hearing preservation and that age was not a significant prognostic factor for hearing preservation rates either. In fact, there was a trend toward improved hearing preservation rates in older patients (56% at < 65 years vs 71% at ≥ 65 years of age; p < 0.1134)\textsuperscript{249}.

In an attempt to distinguish the impact of radiosurgery from the natural course of hearing deterioration, Yomo, Regis and colleagues showed mean annual hearing decrease rates before and after Gamma Knife treatment of 5.39 dB/year and 3.77 dB/year, respectively (p > 0.05). A maximum cochlear dose of less than 4 Gy was found to be the sole prognostic factor for hearing preservation. This study demonstrated the absence of an increase in annual hearing decrease rate after radiosurgery as compared with the preoperative annual hearing decrease rate. There was even a trend indicating a reduction in the annual hearing loss after radiosurgery over the long term\textsuperscript{250}.

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After Gamma Knife radiosurgery in the management of 415 patients with unilateral vestibular schwannoma 65.97% had preservation of serviceable hearing (Pure tone average < or = 50 db and Speech discrimination > or = 50%) at minimum one-year audiological follow-up. The tumors were stable or declining in size in 90.44% of cases\textsuperscript{242}.

Tamura, Regis and colleagues evaluated the long-term hearing preservation after gamma knife radiosurgery for vestibular schwannomas in 74 patients with initially normal or subnormal hearing (Gardner-Robertson Class 1) after a minimum of 3 years of follow-up (median marginal dose was 12 Gy; range, 9-13 Gy). At the time of the last follow-up evaluation, 78.4% of the patients had preserved functional hearing. Tumor control was achieved in 93% of the cases. The probability of preserving functional hearing was higher in patients who had an initial symptom other than hearing decrease (91.1%), in patients younger than 50 years (83.7%), and in those treated with a dose to the cochlea of less than 4 Gy (90.9%)\textsuperscript{251}.

In a separately published analysis, Regis showed that the functional hearing preservation at 3 years is 77.8% when the patient is initially in Gardner-Robertson stage 1, 80% in patients with
tinnitus as a first symptom and 95% when the patient has both. In these patients, the probability of functional preservation at 5 years is 84% \textsuperscript{252}.

Following Gamma Knife radiosurgery for acoustic neuroma in 77 patients who had serviceable hearing (Gardner-Robertson [GR] Class I or II), Kano, Lunsford and colleagues evaluated tumor control and hearing preservation with respect to tumor volume, imaging characteristics, and nerve and cochlear radiation dose; (median tumor volume 0.75 cm\textsuperscript{3}; range 0.07-7.7 cm\textsuperscript{3}, median prescription dose 12.5 Gy; range 12-13 Gy). \textbf{At diagnosis, a greater distance from the lateral tumor to the end of the internal auditory canal correlated with better hearing function. Serviceable hearing was preserved in 71\% of all patients and in 89\% (46 patients) of those with GR Class I hearing. Significant prognostic factors for maintaining the same GR class included pre-SRS GR Class I hearing, a speech discrimination score (SDS) \geq 80\%, a pure tone average (PTA) < 20 dB, and a patient age < 60 years. Significant prognostic factors for serviceable hearing preservation were (all pre-SRS) GR Class I hearing, an SDS \geq 80\%, a PTA < 20 dB, a patient age < 60 years, an intracanalicular tumor location, and a small tumor volume (< 0.75 cm\textsuperscript{3}) \textsuperscript{253}.

Han, Jung and colleagues proposed a classification system based on PTA score and the IL I-V of the auditory brainstem response to predict the rate of hearing preservation in each individual. The mean baseline values for the interlatency (IL) of waves I through V (IL I-V) on auditory brainstem response was determined and the pure tone average was calculated by averaging audiometric masked bone conduction responses at 500 Hz, 1000 Hz, and 2000 Hz in 119 patients with vestibular schwannoma with serviceable hearing who had undergone Gamma Knife treatment. In multivariate analysis, the PTA score and IL I-V were significant and independent factors for hearing preservation: By using the PTA score and IL I-V, the patients were classified into 4 groups with serviceable hearing after SRS being 89.6\%, 64.0\%, 25.8\%, and 6.7\%, respectively \textsuperscript{254}. Others confirmed in a multivariate analysis that pretreatment ipsilateral pure tone average (p < 0.001) was statistically significantly associated with time to non-serviceable hearing \textsuperscript{255}.

Younger GR Class I patients had a significantly higher probability of retaining functional hearing even at the 10-year follow-up: Boari, Mortini and associates studied 379 patients who underwent Gamma Knife radiosurgery for vestibular schwannomas (median clinical follow-up 69.5 months; median tumor volume median 1.2 cm\textsuperscript{3}, range 0.013-14.3 cm\textsuperscript{3}, median prescription dose 13 Gy;
range 11-15 Gy): Control of the tumor with Gamma Knife was achieved in 97.1% of the patients. The overall rate of preservation of functional hearing at the long-term follow-up was 71% for patients with hearing classified as Gardner-Robertson (GR) Class I, and 93% among cases of GR Class I hearing in patients younger than 55 years.

In patients with vestibular schwannoma and well preserved hearing (Gardner-Robertson class I) who had been treated with Gamma Knife radiosurgery, serviceable hearing retention rates (GR grade I or II) were 100% for patients who had no subjective hearing loss before Gamma Knife (n=25). In patients who reported subjective hearing loss before Gamma Knife, serviceable hearing retention rates were 81% at 1 year, 60% at 2 years, and 57% at 3 years after radiosurgery. Patients with a pure tone average (PTA) <15 dB before GKRS had significantly higher rates of preservation of GR class I or II hearing.

At median cochlear maximum doses of 6.9 Gy (range 1.6-16 Gy) and a median audiological follow-up of 35 months (range 6-58 months), the 1-, 2-, and 3-year actuarial rates of maintaining serviceable hearing were 93%, 77%, and 74%, respectively, in 40 patients with vestibular schwannoma with serviceable hearing who had been treated using Gamma Knife surgery. Patients who received a mean cochlear dose less than 3 Gy had a 2-year hearing preservation rate of 91% compared with 59% in those who received a mean cochlear dose of 3 Gy or greater (p = 0.029).

A cohort of 60 patients with unilateral sporadic intracanalicular vestibular schwannomas were studied: at a median follow-up duration of 62 months, the actuarial rates of serviceable hearing preservation were 70%, 63%, and 55% at 1, 2, and 5 years after radiosurgery, respectively. In multivariate analysis, transient volume expansion of ≥20% from initial tumor size was a statistically significant risk factor for loss of serviceable hearing and hearing deterioration, while the cochlear radiation dose did not reach statistical significance.

Delbrouck, Massager and associates studied 415 patients with unilateral vestibular schwannoma who had undergone Gamma Knife radiosurgery. Serviceable hearing was preserved in 65.97% of 144 patients who had serviceable hearing at the time of the treatment (GR class I and GR class II). Of GR class I patients 74.64% preserved serviceable hearing. The tumor was stable or declining in size in 90.44% of cases.

A total of 68 patients with vestibular schwannoma and well preserved hearing (Gardner-Robertson
class I) were treated with Gamma Knife radiosurgery. In patients with no subjective hearing loss, serviceable hearing retention rates (GR grade I or II) were 100% compared with 81% at 1 year, 60% at 2 years, and 57% at 3 years after GKRS for patients with subjective hearing loss. At 2 to 3 years after GKRS, patients without subjective hearing loss or a PTA <15 dB had higher rates of grade I or II hearing preservation).

Threshold Doses for the Preservation of Hearing

In a review of the published literature in 2009 Yang, Parsa and colleagues concluded that patients treated with a prescription dose of 12.5 Gy were more likely to have preserved hearing.

Tamura, Regis and colleagues found that the probability of preserving functional hearing was higher in patients who had been treated with a dose to the cochlea of less than 4 Gy. In 154 patients with vestibular schwannoma who had undergone Gamma Knife surgery Yomo, Regis and colleagues showed that maximum cochlear dose of less than 4 Gy was found to be the sole prognostic factor for hearing preservation. Following Gamma Knife radiosurgery for acoustic neuroma in 77 patients who had serviceable hearing (Gardner-Robertson [GR] Class I or II), Kano, Lunsford and colleagues showed that all patients < 60 years of age who had received a cochlear dose < 4.2 Gy retained serviceable hearing at 2 years post-SRS.

Baschnagel and colleagues found that patients who received a mean cochlear dose less than 3 Gy had a 2-year hearing preservation rate of 91% compared with 59% in those who received a mean cochlear dose of 3 Gy or greater (p = 0.029). No patient who received a mean cochlear dose less than 2 Gy experienced serviceable hearing loss (p = 0.035).

Van Eck and Horstmann had reduced the maximum dose that was applied to the acoustic neuroma to 20 Gy showing that functional hearing was preserved in 83.4% of the patients with functional hearing preoperatively.

The relevance of the mentioned cochlear threshold doses is still questioned by others: In a group of 60 patients (mean marginal dose 12.2±0.1 Gy; range, 11.5-13.0 Gy) the actuarial rates of serviceable
hearing preservation were 70%, 63%, and 55% at 1, 2, and 5 years after radiosurgery, but in multivariate analysis, transient volume expansion of ≥20% from initial tumor size was a statistically significant risk factor for loss of serviceable hearing and hearing deterioration, while the cochlear radiation dose did not reach statistical significance\textsuperscript{259}.

**Malignant Transformation**

In 2014 Seferis performed a search using PubMed and found a total of 29 reported cases of malignant transformation in a vestibular schwannoma after radiation therapy\textsuperscript{261}. The authors also retrieved papers reporting 30 cases of malignant vestibular schwannoma in patients who had not undergone radiation treatment. Of the irradiated cases of malignant transformation, 40.7% were patients with neurofibromatosis. In those cases in which histology showed tumors with previously benign characteristics, the median delay to malignant expression was 72 months. The present meta-analysis indicates that the risk of malignancy over 20 years in cases in which no radiation treatment has occurred is 1.32-2.08 per 100,000, and this risk decreases to 1.09-1.74 per 100,000 if cases of neurofibromatosis are excluded. After radiation treatment, the overall risk over 20 years is 25.1 per 100,000, and this risk decreases to 15.6 per 100,000 if cases of NF are excluded\textsuperscript{261}.

In a previous retrospective cohort study Rowe, Kemeny and colleagues had compared the Sheffield radiosurgery patient database set comprising approximately 5000 patients and 30,000 patient-years of follow-up with national mortality and cancer registries. In this material, a single new astrocytoma was diagnosed, whereas, based on national incidence figures, 2.47 cases would have been predicted. **It was concluded that no increased risk of malignancy was detected in this series**, supporting the safety of radiosurgery. The authors concluded that the risks of radiosurgery-induced malignancy seems small, particularly if such risks are considered in the context of the other risks faced by patients with intracranial pathologies requiring radiosurgical treatments\textsuperscript{262}.

Among 1309 patients with intracranial AVMs treated with Gamma Knife radiosurgery at University of Virginia, Starke, Sheehan and colleagues identified a total of 3 cases of radiosurgically induced neoplasia\textsuperscript{263}. More than 10 years after GKRS, 2 patients were found to have an incidental, uniformly enhancing, dural-based mass lesion near the site of the AVM with radiologic characteristics of a meningioma. As the lesions have shown no evidence of mass effect, they are being followed with
serial neuroimaging. A third patient was found to have neurologic decline from a tumor in immediate proximity to an AVM previously treated with proton beam radiosurgery and GKRS. The patient underwent resection, demonstrating a high-grade glioma. The 3-, 10-, and 15-year incidence of a radiation-induced tumor is 0% (0/812), 0.3% (1/358), and 2.6% (2/78), respectively. The cumulative rate of radiosurgically induced tumors in those with a minimum of 10-year follow-up is 3 in 4692 person-years or 64 in 100,000 person-years. It was concluded that patients had a 0.64% chance of developing a radiation-induced tumor within ≥10 years following GKRS.

Facial Nerve Palsy

Side effects after Gamma Knife radiosurgery of vestibular schwannoma are in fact rare. In 2009 a review of 23 articles representing reporting quantifiable outcome data obtained in 2204 patients who underwent Gamma Knife radiosurgery for vestibular schwannoma showed an overall facial nerve preservation rate of 96.2% (average overall follow-up 54.1 +/- 31.3 months. Patients receiving a prescription dose of ≤ 13 Gy had a better facial nerve preservation rate than those who received higher doses (≤13 Gy = 98.5% vs. >13 Gy = 94.7%, P < 0.0001).

Comparison Gamma Knife vs. Surgery

Myrseth, Lund-Johansen and colleagues conducted a prospective, open, nonrandomized study of treatment-associated morbidity in 91 patients undergoing microsurgery or gamma knife radiosurgery for vestibular schwannomas with a maximum tumor diameter of 25 mm in the cerebellopontine angle. Evidence of reduced facial nerve function (House-Brackmann grade 2 or poorer) at 2 years was found in 46% (13/28) after open microsurgery and in 1.6% (1/60) after Gamma Knife. No patient who underwent surgery had serviceable hearing postoperatively, while 68% of Gamma Knife patients who had serviceable hearing before treatment, preserved serviceable hearing 2 years after treatment. The tinnitus and vertigo visual analog scale score, as well as balance platform tests, did not change significantly after treatment, and working status did not differ between the groups at 2 years. Quality of life (according to the Glasgow Benefit Inventory questionnaire) was significantly better in the GKRS group at 2 years. This prospective
study demonstrated significantly better facial nerve and hearing outcomes after Gamma Knife radiosurgery when compared to open surgery for small- and medium-sized vestibular schwannomas.\textsuperscript{235}

Tamura, Regis and colleagues showed that the risk of dry eye and burning eye was considerably lower in patients after Gamma Knife treatment compared to patients after microsurgery. They used a functional questionnaire to evaluate patient complaints related to the eye and taste in a series of 200 patients 3 years after the Gamma Knife radiosurgery of a unilateral vestibular schwannoma not previously resected. Their answers were compared with those of a group of 200 patients operated on microsurgically. In the microsurgery group 57.6\% of (57/99) presented with permanent postoperative facial nerve palsy while no patient in the Gamma Knife group (0/80) experienced facial nerve palsy. The answers about taste showed that After Gamma Knife 8.1\% of patients complained of a sensation of altered taste while this symptom occurred in 45.5\% of patients after microsurgery.\textsuperscript{265}

Regis, Peragut and colleagues used a patient questionnaire to evaluate the functional outcome and quality of life in a series of 97 consecutive patients with acoustic neuroma treated with Gamma Knife compared with 110 patients in the microsurgery group. Questionnaire answers indicated that 100\% of patients who underwent GKS compared with 63\% of patients who underwent microsurgery, had no new facial motor disturbance and 91\% of patients treated with GKS had no functional deterioration after treatment compared to 61\% in the microsurgery study. The mean hospitalization stay was 3 days after GKS and 23 days after microsurgery. All the patients who underwent GKS who had been employed, except one, had kept the same professional activity (56\% in the microsurgery study). The mean time away from work was 7 days for GKS (130 days in the microsurgery study). Among patients whose preoperative hearing level was Class 1 according to the Gardner and Robertson scale, 70\% preserved functional hearing after GKS (Class 1 or 2) compared with only 37.5\% in the microsurgery group.\textsuperscript{266}

**Combination with Subtotal Resection**

In larger vestibular schwannomas, incomplete resection with planned Gamma Knife radiosurgery
offers the option of reduced morbidity during surgery while maintaining a high degree of local tumor control. In larger acoustic neuromas a combination of surgery and radiosurgery is increasingly applied in order to provide tumor volume reduction, tumor control and functional preservation. Such a combined therapy was shown to be beneficial regarding both tumor control and adverse side effects.

Iwai had published an initial series of 14 patients with large acoustic neuromas using a combination of surgery and radiosurgery. Excellent facial nerve function (House & Brackmann Grade I or II) was preserved in 12 patients (85.7%) in the final follow-up \(^{267}\). Iwai, Yamanaka and colleagues recently (2015) published and update after treatment of 40 patients with large unilateral vestibular schwannomas with planned partial tumor removal followed by Gamma Knife surgery for functional preservation (median maximum tumor diameter 32.5 mm; range 25-52 mm). Gamma Knife was performed 1-12 months after surgical resection (median interval 3 months; median tumor volume at GKS 3.3 cm\(^3\); range 0.4-10.4 cm\(^3\); median prescribed dose 12 Gy; range 10-12 Gy, median follow-up period 65 months; 18-156 months). At the final follow-up, facial nerve preservation (House-Brackmann grade I-II) was achieved in 95%; House-Brackmann grade I: 92.5%, II: 2.5%). Among the 14 patients with preoperative pure tone average (PTA) less than 50 dB, 42.9% maintained PTA less than 50 dB at the last follow-up. Five- and 10-year tumor growth control occurred in 86% of patients \(^{268}\).

Very similar results had been achieved in a small series from Marseille: After subtotal resection of 8 large acoustic neuroma with an initial average maximum diameter of 40 mm (range 35-45), the remaining tumors with a remaining diameter of 18 mm (range 9-20 mm) were treated with Gamma Knife radiosurgery at a mean prescription dose of 11.8 Gy (range 11-13). At a mean follow-up period of 46 months after radiosurgery, excellent facial nerve function (House-Brackmann grade 1 or 2) was preserved in 7/8 patients (87.5%) \(^{269}\).

In 2014 the currently available data were reviewed by Brokinkel, Stummer and colleagues who identified 6 studies comprising 159 patients on the effects of Gamma Knife radiosurgery following subtotal resection of vestibular schwannoma. Gamma Knife surgery was performed on average 6 months postoperatively with a mean marginal dose of 11.88 Gy (mean target volume 4.42 cm\(^3\), mean diameter 18.45 mm). After tumor resection facial nerve function was serviceable (House and
Brackmann Grades I+II) in 82.8% (125/151 patients). Postoperatively hearing was serviceable in 20.2%. Within a mean follow-up time of 50 months, facial nerve function and hearing after incomplete resection remained serviceable in 94.0%, and 11.6%, respectively.

Subtotal surgery can be performed using different techniques and when surgery for a large vestibular schwannoma consists of intracapsular resection and decompression, better preservation of facial and hearing function can be obtained. It was clearly shown by Pan, Yang and colleagues that intracapsular decompression followed by Gamma Knife afforded a better neurological outcome and quality of life than radical extracapsular resection followed by Gamma Knife. In a study comprising 35 patients, the outcomes of intracapsular decompression followed by Gamma Knife surgery (Group I) were compared with outcomes of standard microsurgery followed by radiosurgery (Group II). After the operation, 89% in Group I retained excellent facial function, whereas only 35% in Group II had excellent facial function (p < 0.01). In Group I, 100% retained hearing function after the operation. In Group II, none retained hearing function postoperatively (p < 0.001). No patients experienced adverse effects after GKS. The mean return-to-work times were 2.4 ± 0.16 and 33.4 ± 4.3 weeks in Groups I and II, respectively (p < 0.001). According to the results obtained using the 36-Item Short Form Health Survey (SF-36), patients in Group I enjoyed more significant improvements in quality of life than patients in Group II (p < 0.001).

Pituitary adenomas

In pituitary adenomas medication and microsurgery are typically used as first-line treatments. When hormone-producing tumors cannot be removed completely or when the tumor recurs after surgery, further treatment is imperative in order to stop excess hormone secretion. Previously, fractionated radiotherapy has been applied as alternative treatment, which is currently thoroughly questioned due to a long latency to achieve endocrine normalization, high risk of delayed radiation induced pituitary dysfunction and even secondary tumor development. When hormone-producing tumors cannot be removed completely or when the tumor recurs after surgery, further treatment is imperative in order to stop excess hormone secretion.

Gamma Knife radiosurgery is ideally suited in this situation since the required high radiation doses can be applied locally with an extreme precision while complex treatment planning helps to protect the surrounding structures. In these cases Gamma Knife radiosurgery has been shown to normalize...
the excessive hormone production and stop further tumor growth. Typically, high prescription doses of 25 Gy are applied in hormonally active pituitary adenoma. After radiosurgery, the elevated hormone levels generally decrease slowly within several months. Due to this known latency period, however, stereotactic radiosurgery is generally not preferred over a surgical resection, which ideally provides immediate endocrine normalization. Several studies indicate that withdrawal of anti-secretory medication prior to radiosurgery improves the chance of endocrine remission.

Non-Secreting Pituitary Adenomas

In cases of smaller non-secreting pituitary adenoma Gamma Knife radiosurgery appears to be a safe option providing consistent and reproducible tumor control with very low risk for immediate side effects. Surgery and possibly medication are the main factors in the treatment of pituitary adenomas, but not all symptoms can be abolished and not all tumors stopped with these approaches and not always an endocrinological normalisation is achieved through medication. Recent developments of stereotactic radiosurgery have demonstrated a high local effect allowing reproducible tumor control and even endocrinological normalisation in treatment refractory pituitary adenoma, thus offering a new therapeutical alternative.

In 2013 a systematic review and meta-analysis revealed a total of 17 studies to determine the efficacy and safety of gamma knife surgery for the treatment of nonfunctioning pituitary adenomas. There were significant differences in the rate of tumor control and in the radiosurgery-induced endocrinological deficits depending on the tumor volume (P<0.001)\(^{272}\):

- In patients with tumor volumes <2 ml the rate of tumor control was 99%, the rate of radiosurgery-induced optic neuropathy was 1%, and the rate of radiosurgery-induced endocrinological deficits was 1%\(^{272}\).
- In patients with tumor volumes from 2 to 4 ml rate of tumor control was 96%, the rate of radiosurgery-induced optic neuropathy was 0%, and the rate of radiosurgery-induced endocrinological deficits was 7%\(^{272}\).
- In patients with tumor volumes larger than 4 ml the rate of tumor control was 91%, the rate of radiosurgery-induced optic neuropathy 2%, and the rate of radiosurgery-induced endocrinological deficits was 22%\(^{272}\).
Under the auspices of the North American Gamma Knife Consortium, 9 Gamma Knife surgery (GKS) centers retrospectively combined their outcome data obtained in 512 patients with nonfunctional pituitary adenomas. Overall tumor control was achieved in 93.4% of patients at last follow-up; actuarial tumor control was 98%, 95%, 91%, and 85% at 3, 5, 8, and 10 years postradiosurgery, respectively. Smaller adenoma volume ($p = 0.006$) and absence of suprasellar extension ($p = 0.064$) were associated with progression-free tumor survival. New or worsened hypopituitarism after radiosurgery was noted in 21% of patients, with thyroid and cortisol deficiencies reported as the most common postradiosurgery endocrinopathies. History of prior radiation therapy and greater tumor margin doses were predictive of new or worsening endocrinopathy after GKS. New or progressive cranial nerve deficits were noted in 9% of patients; 6.6% had worsening or new onset optic nerve dysfunction. No patient died as a result of tumor progression.

Several retrospective studies after stereotactic radiosurgery for non-secreting adenoma have shown a successful long-term control: After Gamma Knife treatment with a median minimum treatment dose of 16 Gy a group of 62 patients was followed a median of 64 months. Tumor growth control was 95% at 7 years after radiosurgery with a 5-year risk of developing new anterior pituitary deficits of 18% for patients with a tumor volume of $\leq 4.0 \text{ cm}^3$ compared with 58% for patients with a tumor volume $>4.0 \text{ cm}^3$. No patient had a decline in visual function after a median maximum point dose of 9.5 Gy to the optic apparatus (range, 5.0-12.6 Gy). A previous series of 140 patients with non-secreting pituitary adenoma treated with Gamma Knife radiosurgery (median prescription dose 20Gy) showed no adenoma growth after a median follow-up of 60 months; 89% of treated adenomas decreased in size, with a median volume reduction of 61%. Almost identical results were reported by Mingione, Steiner and colleagues who had treated 100 consecutive patients with non-secretory pituitary macroadenoma (mean prescription dose 18.5 Gy; mean imaging follow-up: 44.9 months). Tumor volume decreased in 65.6% and remained unchanged in 26.7%, and increased in 7.8%. The minimal effective peripheral dose was 12 Gy; peripheral doses greater than 20 Gy did not seem to provide additional benefit. Of 61 patients with a partially or fully functioning pituitary gland and follow-up data, 12 (19.7%) suffered new hormone deficits following Gamma Knife treatment. No neurological morbidity or death was related to treatment.
Park, Kondziolka and colleagues evaluated the outcomes of Gamma Knife radiosurgery in 125 patients with non-functional pituitary adenomas over an interval of 22 years (median target volume 3.5 cm³; range, 0.4–28.1 cm³; median tumor margin dose 13.0 Gy; range, 10–25 Gy). Tumor volume decreased in 53%, remained stable in 37% and increased in 10.4% during a median of 62 months of imaging follow-up. The actuarial tumor control rates at 1, 5, and 10 years were 99%, 94%, and 76%, respectively. Factors associated with a reduced progression-free survival included larger tumor volume (≥ 4.5 cm³) 277.

Another recent study with 48 patients with a nonfunctioning pituitary adenoma performed a median follow-up of 80.5 months after Gamma Knife and a median endocrinological follow-up 95 months, respectively. New hormone deficiency after GKRS occurred in 39%. Overall, control of tumor volume was achieved in 83%. Tumor volume decreased in 75%, was unchanged in 8% and increased in 17%. Tumor volumes greater than 5 cm³ at the time of GKRS were associated with a significantly greater rate of growth (P = .003) compared with an adenoma with a volume of 5 cm³ or less 278.

It is notable that tumor volumes greater than 5 cm³ at the time of GKRS were associated with a significantly greater rate of recurrence 278, since virtually identical results were reported from Pittsburgh, where a larger tumor volume of ≥ 4.5 cm³ resulted in reduced progression-free survival. The actuarial tumor control rates were 94% and 76% after 5 and 10 years, respectively in 125 patients after a median follow-up of 62 months 279. Similarly Pollock showed a threshold of 4.0 cm³ for the 5-year risk of developing new anterior pituitary deficits 274.

In a retrospective review of 62 patients with nonfunctioning pituitary adenomas undergoing Gamma Knife radiosurgery (median tumor volume 4.0 cm³; range, 0.8–12.9; median treatment dose 16 Gy; range, 11–20; median follow-up 64 months; range, 23–161), tumor growth control was 95% at 3 and 7 years after radiosurgery. The 5-year risk of developing new anterior pituitary deficits was 18% for patients with a tumor volume of < or = 4.0 cm³ compared with 58% for patients with a tumor volume >4.0 cm³. No patient had a decline in visual function 274.

Over a period of 10 years 140 patients with nonsecreting pituitary adenoma were treated by Gamma Knife at Na Homolce Hospital, Prague with 79 patients being followed up for longer than 3 years
(median prescription dose 20Gy; range 12-35 Gy, median follow-up 60 months (range 36 -122 months). No adenoma growth was detected; 89% of treated adenomas decreased in size, with a median volume reduction of 61%. There was no vision impairment after radiosurgery, while 4 out of 52 patients with abnormal perimeter vision reported improvement \(^{275}\).

In a long-term follow-up 23 patients with non-functioning pituitary adenomas (median volume 1.1 cm\(^3\); median prescription dose 20 Gy) were followed at a median of 78 months with MR imaging and 97 months clinically. Tumor growth control was 100%, One recurrence was discovered outside radiation field and no new hypopituitarism was developed \(^{280}\).

**Side effects: Visual Dysfunction**

An analysis of 217 patients with recurrent secretory (n = 131) and non-secretory (n = 86) pituitary adenomas treated with Gamma Knife surgery was performed to determine the incidence of and risk factors for subsequent development of visual dysfunction. Nine patients (4%) developed new visual dysfunctions, and these occurred within 6 hours to 34 months following radiosurgery. Three of these patients had permanent deficits whereas in 6 the deficits resolved. Prior GKS or radiotherapy (in 5/9) resulted in a significant increase in the incidence of cranial nerve dysfunction \(^{281}\).

**Threshold Doses**

Specific structures in the brain have specific tolerances for the applied radiation. This is particularly important in the treatment of tumors close to the optic system.

A retrospective review of 222 patients having Gamma Knife radiosurgery for benign tumors adjacent to the anterior visual pathway concluded that the chance of radiation-induced optic neuropathy according to the maximum radiation dose received by the anterior visual pathway was 0% below 12Gy and 10% (95% CI 0-43.0%) for patients receiving >12 Gy, respectively. One patient (0.5%) who received an unusually high maximum radiation dose of 12.8 Gy to the anterior visual pathways had developed unilateral blindness 18 months after SRS \(^{282}\).

Another retrospective review from the same team around Pollock compared visual function before and after SRS in 133 patients (266 sides) with pituitary adenomas having SRS showed risks of developing a radiation-induced optic neuropathy at the 8-Gy, 10-Gy, and 12-Gy volumes (95%
confidence interval) of 0% to 2.6%, 0% to 4.7%, and 0% to 13.9%, respectively. The conclusion was that patients without prior radiation treatments can safely receive radiation doses up to 12 Gy with a low risk of radiation-induced optic neuropathy.\textsuperscript{283}

Marek, Liscak and colleagues reported that hypopituitarism after Gamma Knife developed only in 2.2% of patients irradiated with a mean dose to pituitary <15 Gy in contrast to 72.5% patients irradiated with a mean dose to pituitary >15 Gy.\textsuperscript{284}

In another analysis a significant increase of new endocrine insufficiencies was seen at doses when 6.5 Gy were applied to the pituitary stalk (vs. 4.1 Gy) ($p = 0.004$) and when more than 12.4 Gy was applied to the pituitary gland ($p = 0.05$). That has been found after analysis of 108 Gamma Knife-treated patients with pituitary adenoma where spot dosimetry was used to determine doses delivered to structures of the hypothalamopituitary axis. The overall tumor control rate was 97% and the endocrinological cure rate was 61.2%. The results of this study show that patients in whom the pituitary stalk and pituitary gland receive a high mean point dose are more likely to develop pituitary insufficiencies after GKS than those who receive a lower dose.\textsuperscript{285}

---

Tab 1. Gamma Knife radiosurgery for non-secreting pituitary adenoma

<table>
<thead>
<tr>
<th>Years of treatment</th>
<th>Number of patients</th>
<th>Tumor volume (cm(^3))</th>
<th>Prescription doses</th>
<th>Months of FU</th>
<th>complications</th>
<th>Tumor control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pollock BE, et al. Int J Radiat Oncol Biol Phys. 2008 Apr 1;70(5):13</td>
<td>1992-2004</td>
<td>62</td>
<td>4 (0.8-12.9)</td>
<td>16 Gy (11-20)</td>
<td>64 (median)</td>
<td>32 % risk of pituitary deficit at 5y no visual deficit</td>
</tr>
</tbody>
</table>
Gamma Knife Radiosurgery as Primary Management of Non-Secreting Pituitary Adenomas

In general, the initial treatment in pituitary adenomas is surgical removal. With regard to the favorable results after stereotactic radiosurgery however, it has been discussed if Gamma Knife radiosurgery can be applied as first line treatment in uncomplicated non-secretory pituitary adenomas.

Among a total of 569 patients who were treated using Gamma Knife radiosurgery for nonfunctioning pituitary adenomas, 41 patients underwent Gamma Knife treatment as primary management because of an advanced age, multiple comorbidities, or patient preference. Patients received a median tumor margin dose of 12 Gy (range 6.2-25.0 Gy) at a median isodose of 50%. The overall tumor control rate was 92.7%, and the actuarial tumor control rate was 94% and 85% at 5 and 10 years post-radiosurgery, respectively. New or worsened hypopituitarism developed in 24% at a median interval of 37 months after GKRS. Delayed hypopituitarism was observed more often in patients who had received a tumor margin dose > 18 Gy (p = 0.038) and a maximum dose > 36 Gy (p = 0.025). One patient suffered new-onset cranial nerve palsy. No other radiosurgical complications were noted 286.

Acromegaly

Acromegaly affects 86–240 individuals per million 287. Recently the results of the German Acromegaly register comprising 1344 patients followed in 42 centers were published: 89% of the patients had at least one surgical intervention, but after surgery only 38.8% of the patients were controlled without further therapy and among the medically treated patients 65.2% were controlled 288. In general three
types of drugs are used for patients with acromegaly and postoperative persistent hormonal activity dopamine agonists (DAs) like bromocriptine and cabergoline, somatostatin receptor ligands (SSAs) such as octreotide LAR and lanreotide and GH receptor antagonists (GHRH) such as pegvisomant. However, of 557 medically treated patients with acromegaly, 65.2% had a normal IGF1 and 86% had at least one operation, 28% were operated and had received adjunctive radiotherapy.

Since neither anti-secretory drugs nor surgical adenoma resection will guarantee endocrine normalization in all cases of pituitary adenoma, there is need for an additional treatment option such as radiosurgery.

After conventional fractionated radiotherapy for acromegaly endocrinological normalization could be achieved in some patients, but there is a very long latency between radiotherapy and effect: Jenkins and colleagues reported in a very large multicenter study of 884 patients from 14 centers throughout the United Kingdom a normalization of serum GH (< 2.5 mg/L) in 22% at 2 years and 60% at 10 years. Barrande demonstrated hormonal normalization in 7% of his patients at 2 years, in 35% at 5 years and in 53% 10 years after treatment. A long-term study of 72 acromegalic patients treated with fractionated radiotherapy showed that normal age-matched IGF-I levels were reached in 16% after 10 years.

The side effects induced by fractionated radiotherapy were significant: The risk for secondary radiation induced hypopituitarism increased progressively after radiotherapy and 10 years after radiotherapy, 80% of the patients had gonadotropic deficiency, 78% showed thyrotropic insufficiency, and 82% had developed a corticotropic deficiency.

Epaminonda demonstrated secondary radiation induced tumors in 4.5% of patients with acromegaly 9-22 years after conventional fractionated radiotherapy, which was confirmed by others.

**Stereotactic radiosurgery of acromegaly**

In 2010 Yang and colleagues performed a comprehensive search of the English language literature revealing 970 patients published between June 1998 and September 2009 with new, recurrent, or persistent acromegaly who had been treated using radiosurgery with assessable and quantifiable outcome data. The review showed an overall disease control rate without medication in 48%-53%, while the overall disease control rate with or without medication was 73% at a mean reported follow-up of 48.5 ± 25.8 months (mean overall tumor volume 2.11 ± 1.16 cc). Others showed a
rate of remission of 58.3% at 5 years in 103 acromegalic patients treated with Gamma Knife. Further 14.6% were in remission after Gamma Knife while on treatment with somatostatin analogues. No serious side effects occurred after GK.

A similar remission rate of 54.5% was achieved after 60 months of follow-up in 22 patients with acromegaly treated at the Endocrinology-Metabolism Clinic of Cerrahpasa Medical School in Istanbul. Tumor growth was well controlled in 95.2%.

Castinetti, Brue and colleagues followed 82 patients with acromegaly prospectively studied over a decade, with a mean follow-up of 49.5 months showing that 17% percent of the patients were in remission without any treatment and 23% previously uncontrolled on somatostatin agonists fulfilled the same criteria after Gamma Knife while maintained on medical treatment. J Clin Endocrinol Metab. 2005 Aug;90(8):4483-8. Epub 2005 May 17. Outcome of gamma knife radiosurgery in 82 patients with acromegaly: correlation with initial hypersecretion. Castinetti F, Taieb D, Kuhn JM, Chanson P, Tamura M, Jaquet P, Conte-Devolx B, Régis J, Dufour H, Brue T.

Endocrine remission was achieved in 47.5 % and endocrine control in additional 10.0 % after Gamma Knife radiosurgery at the University of Pittsburgh in a series of patients with acromegaly (n= 40; median follow-up 72 months; range 24-145). Patients with lower IGF-1 level and with tumors that were less invasive of the cavernous sinus before GKRS were associated with better GH remission rates. Imaging-defined local tumor control was achieved in 97.5 %, while 40.0 % eventually developed a new pituitary axis deficiency at a median onset of 36 months after radiosurgery. No patient developed new visual dysfunction. Almost one half of the patients no longer required long term medication suppression.

Adenoma Subtypes

While patients who have a sparsely granulated somatotroph-cell adenoma may be less responsive to medical therapy, they exhibited similar responses to Gamma Knife radiosurgery as patients with a densely granulated somatotroph-cell adenoma adenoma. After Gamma Knife radiosurgery the actuarial remission rates in the densely granulated somatotroph-cell adenoma group at 2, 4, and 6 years post-radiosurgery were 35.1, 71.4, and 79.3 %, respectively, while those in sparsely
granulated somatotroph-cell adenoma group were 35.4, 73.1, and 82.1%, respectively.  

**Latency of Endocrinological Normalisation**

In a retrospective long-term analysis with a median follow-up of 10 years after Gamma Knife treatment of acromegalic patients it was demonstrated that cure rates improved over time to 46% at 10 years. Normal IGF-I values were observed in 82% of patients at their last visit. No visual impairment, disease recurrence, tumor growth or secondary cerebral tumor occurred.  

Liu, Lunsford and colleagues found gradually increasing endocrine remission rates of 18.6%, 44.5% and 67.6% at 3, 5 and 7 years after radiosurgery, respectively. The team from Bergen showed that normal IGF-I levels were achieved in 45% 3 years after Gamma Knife radiosurgery, 58% after 5 years, and in 86% after 10 years. Virtually identical results were published by Jezková and colleagues from the Gamma Knife group in Prague with a normalization of serum GH (< 2.5 μg/l) in 23.9% 1 year after radiosurgery, in 47.1% at 2 years, in 67.4% at 5 years and 85.7% 8 years after treatment. In general Gamma Knife radiosurgery resulted in endocrine normalization (defined as GH values <2.5 ng/ml, and normalization of the age and gender appropriate IGF 1) in 40-60% between 2 and 5 years after radiosurgery. The results demonstrate a faster endocrine normalization after Gamma Knife when compared to fractionated conventional radiotherapy, which previously had been demonstrated by Landolt, who showed that the mean time to endocrine normalization was 1.4 years Gamma Knife cohort and 7.1 years in the group treated with fractionated radiotherapy with significant difference.  

Sheehan and colleagues reviewed a total of 418 patients who underwent Gamma Knife radiosurgery at the University of Virginia with a median follow-up of 31 months (median 31 months) showing that in patients with a secretory pituitary adenoma, the median time to endocrine remission was 48.9 months. In 90.3% of patients there was tumor control.  

**Radiosurgical Salvage Treatment after Failed Conventional Radiotherapy**

A cohort of 25 patients with pituitary adenomas who had not responded to a previous treatment of
conventional external beam radiotherapy was treated with Gamma Knife radiosurgery. Following GK, mean GH fell by 49% at 1 year in patients with somatotroph tumors. Serum IGF1 fell by 32% at 1 year and by 38% at 2 years. At final investigation, 80% of the patients with acromegaly have achieved normalisation of IGF1, and 30% have also achieved a mean GH level of <1.8 ng/ml correlating with normalised mortality. Prior to GK, 72% of the patients were panhypopituitary, and 42% of the remainder developed new anterior pituitary hormone deficiencies. No other adverse events have been detected at a mean follow-up of 36.4 months 307.

Radiation Doses

Typically, rather high prescription doses of >25 Gy directed to the tumor margin are applied in hormonally active pituitary adenoma. However, two series could not establish a relation between outcome in acromegaly and doses after median doses of 21 Gy 300 and 30 Gy 308. Relative low doses (median 18.9Gy) were given in a series by Kobayashi and colleagues with slightly less effective outcome 309. Further studies will have to elucidate if prescription doses can be reduced without increasing the risk of therapeutic failures.

Kobayashi, Fujitani and colleagues concluded that normalization of GH and IGF-1 secretion was difficult to achieve in cases with large tumors and low-dose radiation. They had treated 67 patients for residual or recurrent growth hormone (GH)-producing pituitary adenomas using Gamma Knife radiosurgery (mean tumor volume 5.4 cm3) and applied a relatively low mean margin dose of 18.9 Gy. After a mean follow-up duration of 63.3 months (range 13-142 months) the tumor response rate was 68.3%, and the control rate 100%. Growth hormone was normalized (GH < 1.0 ng/ml) in 4.8%, was nearly normal in 11.9% (< 2.0 ng/ml) and significantly decreased (< 5.0 ng/ml) in 23.8%, decreased in 21.4%, unchanged in 21.4%, and increased in 16.7%. Serum insulin-like growth factor (IGF)-1 was significantly decreased (IGF-1 < 400 ng/ml) in 40.7% 309.

Relevance of Pre-operative Hormonal Levels

Similarly to a previously cited study after conventional fractionated radiotherapy 291, Jeskova found that the less active adenomas were normalized earlier and the effect of Gamma Knife treatment depended on the baseline hormonal activity of the adenoma with impact of the levels of GH and more significantly of IGF-1 304. Similarly Pollock and colleagues demonstrated a lower pre-Gamma
Knife IGF-1 level (less than 2.25 times the upper limit) was associated with a higher likelihood of endocrine remission\textsuperscript{310}.

**Radioprotective Effect of Anti-Secretory Therapy**

Landolt had found that withdrawal of somatostatin suppression prior to Gamma Knife improves the chance of endocrine remission\textsuperscript{311}, which has been corroborated by others\textsuperscript{310,312}. As a practical policy, it is currently recommended to suspend all anti-secretory medication before radiosurgery.

**Side Effects in Radiosurgery of Pituitary Adenoma**

Treatment induced secondary hypopituitarism can appear very late, and has been described between 6–74 months after Gamma Knife treatment\textsuperscript{308}. The Pittsburgh Gamma Knife group reported pituitary deficit in 34\% after a median of at 36 months\textsuperscript{300} and Pollock described a 33\% risk of pituitary deficit after 5 years\textsuperscript{313}. This highlights the need for long-term clinical control of patients with radiotherapeutical or radiosurgically treated pituitary adenoma.

Hence, secondary hypopituitarism with hormonal deficiency is a phenomenon and problem affecting all forms of radiation of the hypophysis at various degrees. The reason for radiation induced functional defects is still a matter of intense discussion. Feigl and colleagues had initially demonstrated that the pituitary stalks in patients with deterioration of pituitary function received a statistically higher dose of radiation, 7.7 +/- 3.7 Gy compared with 5.5 +/- 3 Gy (p = 0.03) after spot dosimetry was performed in the hypothalamic region, the pituitary gland, and pituitary stalk in 59 patients following gamma knife radiosurgery for pituitary adenomas\textsuperscript{314}.

The Gamma Knife group in Prague concluded that rather the radiation dose applied to the adjacent pituitary gland is responsible for late deficits since in the group of patients developing hypopituitarism, the mean dose on the adjacent pituitary gland was significantly increased 35.4 Gy (17.4–63.1Gy). No T4 or sex hormone deficiency developed if the medium pituitary dose did not exceed 15 Gy, and no cortisol deficiency developed if the medium dose was below 18 Gy\textsuperscript{308}. The cumulative risk of adrenocortical deficiency development was calculated at 85\% after 90 months when the mean dose on the healthy pituitary exceeded 20 Gy\textsuperscript{308}. The same group applied these dose thresholds prospectively in patients with pituitary adenoma, where the dose to the pituitary gland was reduced to <15 Gy which resulted in a reduction of hypopituitarism after Gamma Knife
treatment to only 2.2% (1/45), in contrast to 72.5% of patients who had been irradiated with a mean dose >15 Gy to the pituitary gland.

**Tab 5. Gamma Knife radiosurgery for Acromegaly**

<table>
<thead>
<tr>
<th>Years of treatment</th>
<th>Number of patients</th>
<th>Tumor volume</th>
<th>Prescription doses</th>
<th>Months of FU</th>
<th>Endocrine complications</th>
<th>Normalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Franzin A, et al.</td>
<td>1994-2009</td>
<td>103</td>
<td>3.1 in 77%</td>
<td>71</td>
<td>7.8% pituitary deficit</td>
<td>58.3% at 5 years</td>
</tr>
<tr>
<td>Int J Endocrinol.</td>
<td></td>
<td></td>
<td>0.68 in 23%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2012;2012:342034.</td>
<td></td>
<td></td>
<td>21 Gy (12-30)</td>
<td></td>
<td>34% pituitary deficit</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>22 Gy (mean)</td>
<td></td>
<td>4.2% visual deficit</td>
<td></td>
</tr>
<tr>
<td>Liu X, et al.</td>
<td>1988-2009</td>
<td>40</td>
<td>2</td>
<td>72 median</td>
<td>34% pituitary deficit</td>
<td>47.5%</td>
</tr>
<tr>
<td>J Neurooncol. 2012</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jagannathan J, et al.</td>
<td>1988-2006</td>
<td>95</td>
<td>1.23 (0.01-6.6)</td>
<td>57 (mean)</td>
<td>34% pituitary deficit</td>
<td>53% at median</td>
</tr>
<tr>
<td>Neurosurgery. 2008</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.2% visual deficit</td>
<td>23.5 months</td>
</tr>
<tr>
<td>Jun;62(6):1262-96-9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vik-Mo EO, et al.</td>
<td>1993-2003</td>
<td>53</td>
<td>3.3 (0.5-18)</td>
<td>63 (median)</td>
<td>33% risk of pituitary</td>
<td>60% at 5 years</td>
</tr>
<tr>
<td>Eur J Endocrinol. 2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>deficit after 5y</td>
<td>w/o medication</td>
</tr>
<tr>
<td>Sep;157(3):255-63</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Pollock BE, et al.</td>
<td>1991-2004</td>
<td>46</td>
<td>1.35 (0.09-12.7)</td>
<td>53.7 (mean)</td>
<td>31% thyroidal deficit</td>
<td>50% at 54 mo</td>
</tr>
<tr>
<td>J Neurosurg. 2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14% adrenal deficit</td>
<td></td>
</tr>
<tr>
<td>May;106(5):833-8.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>41% gonadal deficit</td>
<td></td>
</tr>
<tr>
<td>Jezková J, et al.</td>
<td>after 1993</td>
<td>96</td>
<td>5.4</td>
<td>63.3 (mean)</td>
<td>14.6% risk of pituitary</td>
<td>40.7%</td>
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<tr>
<td>Clin Endocrinol (Oxf).</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>deficit</td>
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<td>May;64(5):588-95.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Castinetti F, et al.</td>
<td>1993-2003</td>
<td>84</td>
<td>not given</td>
<td>49.5</td>
<td>17% risk of pituitary</td>
<td>40% at mean 36 mo</td>
</tr>
<tr>
<td>J Clin Endocrinol Metab. 2005 Aug;90(8):4483-8.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>23% normalized with medication</td>
<td></td>
</tr>
<tr>
<td>Kobayashi T, et al.</td>
<td>after 1991</td>
<td>67</td>
<td>18.9 Gy</td>
<td>63.3 (mean)</td>
<td>14.6% risk of pituitary</td>
<td>40% at 54 mo</td>
</tr>
<tr>
<td>J Neurosurg. 2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>deficit</td>
<td></td>
</tr>
<tr>
<td>Suppl:119-23.</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Prolactinoma

About 40% and thereby the most common of all pituitary adenomas are prolactinoma with a prevalence ranging between 6–50 per 100,000 \(^{315}\). Hyperprolactinemia interrupts the pulsatile secretion of gonadotrophin-releasing hormone, inhibits the release of luteinizing hormone and follicle-stimulating hormone, and directly impairs gonadal steroidogenesis \(^{316}\). Sometimes mixed growth hormone and prolactin-secreting tumors can occur, presenting as acromegaly in together with hyperprolactinemia \(^{316}\).

Prolactinoma can be large, but medical therapy using dopaminergic agonists such as bromocriptine and cabergoline are first-line treatment even for prolactin macroadenoma. In many cases the medication alone reduces the tumor volume and restores the pituitary function \(^{316}\). In microprolactinoma the primary treatment goal is to restore gonadal function by normalizing prolactin levels \(^{316}\).

A fraction of prolactinomas are resistant to dopamine agonist therapy and a trans-sphenoidal tumor resection should be considered in symptomatic patients, who cannot tolerate high doses of cabergoline or who are not responsive to dopamine agonist therapy \(^{315}\).

A recent study evaluated the endocrinological efficacy of transsphenoidal surgery in prolactinoma patients reporting typical results with postoperative remission in 63% of microprolactinomas and 60% of noninvasive macroprolactinomas, and none of the invasive macroprolactinomas. Better remission rate was independently predicted by lower diagnostic prolactin levels and by the lack of abnormal postoperative residual tissue (P<0.05). A recurrence of hyperprolactinemia was observed in 34% of patients after a median follow-up period of 36 (7-164) months \(^{317}\). The success rate of surgery appears to be higher for patients with prolactin levels lower than 200μg/l (4000 mIU/l) \(^{316}\).

In rare patients who fail both medical treatment and surgical resection, radiation therapy of prolactinoma can be considered.

**Gamma Knife Radiosurgery for Prolactinoma**

Prolactinomas are generally treated with dopamine agonists, which induce both tumor volume regression and endocrine remission. In case of failures of the medical therapy, some tumors are
resected. When both medication and surgery fails, stereotactic radiosurgery may be a remaining option. Radiosurgery may provide some endocrine improvement in a number of patients, but the rates for complete endocrinological normalization and the number of patients with complete remissions after stereotactic radiosurgery are limited. Endocrine normalization has been defined as normal serum prolactin <20 ng/ml, in the absence of dopamine agonist therapy 318. Prolactinoma are generally considered an endocrine disease and a direct relationship between imaging outcomes and endocrine remissions are not always observed. At higher radiation doses 73.1% of macro-prolactinoma decreased in size 319. In a recent series from Charlottesville, Virginia, 46% of patients achieved at least a 20% reduction of their in tumor size and 43% of patients had a stable tumor volume on follow-up, while endocrine normalization was achieved in 37.1% 318. In 2015 an update was published by the same group, now with a total of 38 patients with prolactinoma who had been treated with Gamma Knife radiosurgery at the University of Virginia and endocrine remission was achieved in 50 %. GKRS induced hypopituitarism occurred in 30.3 % 320. In a recent series from Pittsburgh endocrine normalization was achieved in only 27% with improvement in 54% after using rather low median marginal (prescription) doses of 15Gy. In univariate analysis, a prolactin level less than 200 ng/ml before Gamma Knife treatment were associated with higher rate of endocrine normalization 321. A virtually identical outcome was reported by the group from Charlottesville with endocrine remission in 26% after slightly higher prescription doses of 18.6 Gy 318, while Tanaka, Pollock a and colleagues reported a 4-year actuarial rate of normalization in 17% and additional 14% of patients with normal serum prolactin while on dopamine agonist medication 322.

The Gamma Knife group in Prague used considerably higher radiation doses with a median prescription dose of 34 Gy (range 20-49 Gy) and reported a higher response rate with 37.1% of patients with endocrine normalization and 42.9 % normal serum prolactin during continued medication 319. Similarly, others had shown that margin tumor dose of 30 Gy or more seemed to be associated with a higher endocrinological normalization rate 323. Two series demonstrated a better outcome after radiosurgery for smaller prolactinoma with volumes of less than 3cc 318,324. The average time to remission was 24.5 months ranging between 8 and 48 months 318 and 11.5 months (range 2–42 months) in another recent series 324. In line with the other types of pituitary adenoma, it was demonstrated even for prolactinoma, that antisecretory medication with dopamine agonists during Gamma Knife treatment was associated
with a lower rate of remission\textsuperscript{318}, which was not confirmed by Jezkova and colleagues\textsuperscript{319}. In summary, the radiosurgical results after Gamma Knife treatment of prolactinoma show a normalization only in a minority of patients with better outcome for smaller tumors (<3cc)\textsuperscript{318,321}, higher prescription doses\textsuperscript{319,323} and in patients where the anti-secretory medication was suspended during radiosurgery.

Tab 6. Gamma Knife radiosurgery for Prolactinoma

<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Years of treatment</th>
<th>Number of patients</th>
<th>Tumor volume (cm\textsuperscript{3})</th>
<th>Prescription doses</th>
<th>years of FU</th>
<th>complications</th>
<th>Endocrine Normalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu X, et al.</td>
<td>1994-2009</td>
<td>22</td>
<td>3 (0.3-11.6)</td>
<td>15 Gy (12–25 Gy)</td>
<td>36 months (12–185).</td>
<td>3/22 delayed tumor progression</td>
<td>27.3% normalization 54.5% endocrine improvement</td>
</tr>
<tr>
<td>Tanaka S. et al.</td>
<td>1994-2006</td>
<td>22</td>
<td>2.2 (0.4-29)</td>
<td>25 Gy (16–30 Gy)</td>
<td>60 mo (16-129)</td>
<td>42% new anterior pituitary deficits was at 4 years</td>
<td>17% 4-year actuarial rate of normalization 14%normal serum PRL on dopamine agonist med.</td>
</tr>
<tr>
<td>Jezková J, et al.</td>
<td>1993-2005</td>
<td>35</td>
<td>0.9cc</td>
<td>34 Gy (20-49 Gy)</td>
<td>66 mo (median)</td>
<td></td>
<td>37.1% normalization 42.9 %normal serum PRL on dopamine agonist med.</td>
</tr>
<tr>
<td>Pouratian N, et al.</td>
<td>1990-2003</td>
<td>23</td>
<td>18.6 Gy (0.3–25) Gy</td>
<td></td>
<td>55mo</td>
<td>29% new anterior pituitary deficits after mean of 44 months (33–51 mo).</td>
<td>26% after average 24.5mo (8-48)</td>
</tr>
<tr>
<td>Pan L, et al.</td>
<td>1993-1997</td>
<td>128</td>
<td>31.2 Gy mean (9-35 Gy)</td>
<td></td>
<td>33.2 mo mean (6-72)</td>
<td></td>
<td>52% &quot;clinical cure&quot;</td>
</tr>
</tbody>
</table>
Cushing’s disease

Due to the rarity of the condition, the published series after stereotactic radiosurgery for Cushing’s disease are rather small and only few studies report more than 20 patients. Three series report the results of stereotactic radiosurgery for Cushing’s disease after treatment with Gamma Knife with subsequent endocrine normalization in 35%-63%. In the largest available study from Charlottesville, Virginia, Jagannathan described that normal 24-hour urinary free cortisol levels were achieved in 54% (49 patients), at an average time of 13 months after treatment (2–67 months), however 20% experienced a relapse of Cushing’s disease after initial remission at a median of 27 months. The mean prescription dose in these patients was 22 Gy.

In 2010 a published review of the literature provided a total of 29 published series that have reported the results for 445 patients with Cushing’s disease treated with postoperative radiosurgery or with primary radiosurgery. The mean radiosurgical margin dose (i.e. dose to the margin of the adenoma) for these series ranged from 14.7 to 32 Gy. Exclusion of series with less than 10 patients and less than 2-years follow-up resulted in endocrine remission rates from 17–83% and remission is usually observed within 1–2 years. Published tumor control rates range from 50–100%.

The visibility of the adenoma in patients with Cushing’s disease can be an issue and accordingly, the tumor cannot always be outlined on the planning MR image. Without an accurate target, the efficacy of stereotactic radiosurgery is significantly compromised. Hormone deficiencies after Gamma Knife occurred in 22% at a mean of 16 months after radiosurgery (4–36 months). In 5 patients (5.6%) and ophtalmoplegia developed after radiosurgery, in 4/5 patients had previously undergone radiosurgical procedures.

Kobayashi reported a normalization of endocrine levels patients (<50 pg/ml for ACTH level and < than 10 microg/dl for serum cortisol) in 35% of patients with additional significantly improved levels in additional 25% after Gamma Knife treatment of Cushing’s disease at mean margin dose of 28.7 Gy (range 15–70 Gy) in relatively large adenomas with mean volume of 3.24 cm³ (0.07–10.5 cm³). A high control rate of 83.2% was achieved when the maximum dose was higher than 55 Gy and/or
a margin dose exceeded 40 Gy, thus indicating the importance of applied doses\textsuperscript{326}. Castinetti and colleagues reported similar results after Gamma Knife treatment with normalization in 42.5\% after a mean of 22 months \textsuperscript{329}. The target volume was significantly smaller in patients where remission could be achieved (0.44 vs. 0.91 cm\textsuperscript{3}). Interestingly, patients who were off anticortisolic drugs at the time of Gamma Knife had a better chance of remission (48\% vs 20\%) \textsuperscript{329}. The phenomenon of potential radioprotection by anti-secretory drugs has also been described in the treatment of acromegaly.

The additive effect of radiation has to be considered when patients are treated with either repeated radiosurgery or with a combination of fractionated radiotherapy and radiosurgery: so far no stratified dose escalation studies are available but in the Charlottesville series 5 patients (5.6\%) developed ophtalmoplegia after radiosurgery, four of these five patients had previously undergone radiosurgical procedures \textsuperscript{325}. In 2013 Sheehan published a retrospective review of 96 patients with Cushing's disease treated with Gamma Knife surgery the University of Virginia (mean tumor margin dose 22 Gy; median follow-up 48 months; range 12-209.8 months) and showed that remission of Cushing's disease occurred in 70\% of patients \textsuperscript{330}. The median time to remission among all patients was 16.6 months (range 1-165.7 months). The median time to remission in those who had temporarily stopped taking ketoconazole at the time of Gamma Knife was 12.6 months, whereas it was 21.8 months in those who continued to receive ketoconazole (p < 0.012). Tumor control was achieved in 98\% of patients. New loss of pituitary function occurred in 36\% of patients. New or worsening cranial neuropathies developed in 5 patients after GKS, with the most common involving cranial nerves II and III \textsuperscript{330}. Similarly, hormonal normalization was reached in 80.7\% of 26 patients with Cushing's disease who had been followed-up after Gamma Knife radiosurgery in Prague. The median time to normalization was 30 months (6-54 months) \textsuperscript{331}.

In summary, stereotactic radiosurgery offers an additional option in the treatment of surgically therapy refractory patients with Cushing's disease. It has to be considered that the adenoma has to be visible on the stereotactic pre-treatment MRI and that relatively high prescription doses have to be applied. Series with lower prescription doses or impaired diagnostic visibility provide
lower therapeutic effects. Normalization of endocrine levels patients ( <50 pg/ml for ACTH level and < than 10 microg/dl for serum cortisol) in 35% of patients with additional significantly improved levels in additional 25% can be expected. Empirically established threshold doses of optic nerves, chiasm and cranial nerves have to be considered in particular when several radiation treatments are applied. Potential side effects comprise secondary endocrine deficits that may appear several years after radiosurgery. The risk for other clinical side effects is low after stereotactic radiosurgery.

Nelson's syndrome

Nelson’s syndrome is a significant and frequent risk for patients with Cushing’s disease who undergo bilateral adrenalectomy. Gamma Knife appears to provide prophylaxis for Nelson's syndrome when used before bilateral adrenalectomy 332.

Whole-Sellar Stereotactic Radiosurgery

Functioning pituitary adenomas (FPAs) can be difficult to delineate on postoperative magnetic resonance imaging, making them difficult targets for stereotactic radiosurgery. In such cases, Gamma Knife treatment with radiation delivery to the entire sella has been utilized as a radiosurgical equivalent of a total hypophysectomy in 64 patients with acromegaly, Cushing disease and prolactinoma (median margin dose of 25 Gy, n=64; median endocrine follow-up 41 months) The 2-, 4-, and 6-year actuarial remission rates were 54%, 78%, and 87%, respectively. New-onset neurological deficit was found in 6.3%, new-onset hypopituitarism in 43.5% 333.

Second Intervention after Failed Resection in Cushing’s Disease

Fifty-two patients with relapse of Cushing’s disease after transsphenoidal adenomectomy were enrolled and randomly underwent a second surgery or Gamma knife radiosurgery as the next therapeutic approach. The statistical analysis showed higher recurrence-free interval in the Gamma knife group compared with the transsphenoidal adenomectomy group 334.
Tab 3. Gamma Knife radiosurgery for Cushing’s disease

<table>
<thead>
<tr>
<th>Years of treatment</th>
<th>Number of patients</th>
<th>Tumor volume (cm$^3$)</th>
<th>Prescription doses</th>
<th>Months of FU</th>
<th>complications</th>
<th>Endocrine Normalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castinetti F. et al Eur J Endocrinol. 2007 Jan;156(1):91-8</td>
<td>1993-2003</td>
<td>40</td>
<td>0.5</td>
<td>29.5 Gy (median 15-40)</td>
<td>54.7 mo (mean)</td>
<td>15 % new endocrine deficit</td>
</tr>
<tr>
<td>Sheehan JM, et al. Neurosurg. 2000 Nov;93(5):738-42.</td>
<td>1990-1998</td>
<td>43</td>
<td>not given</td>
<td>not given</td>
<td>44</td>
<td>16 % new endocrine deficit 2.3 % visual deficit</td>
</tr>
</tbody>
</table>
**Gamma Knife Radiosurgery for Malignant Gliomas and Glioblastomas**

Glioblastoma (GBM) is the most common primary CNS tumor in the USA and European countries. The incidence rate for glioblastoma per 100,000 population/year is 3.32 in males and 2.24 in females. Population-based studies report that the overall survival of patients with newly diagnosed GBM is 17–30% at 1 year, and only 3–5% at 2 years, despite access to state-of-the-art modalities of therapy. Observed survival rates in 715 patients with glioblastoma (2004) were 42.4% at 6 months, 17.7% at 1 year, and 3.3% at 2 years. According to the SEER database that collects cancer incidence and survival data representing 28% of the US population, the median survival time of adult patients with glioblastoma was 9 months in 2010.

Standard therapy of malignant glioma and glioblastoma consists of surgical resection, radiotherapy and chemotherapy. It appears that tumor recurrences are inevitable in glioblastoma.

Initial Retrospective evidence appeared to suggest that the survival of patients who were treated with a radiosurgery boost was superior to historical series in particular for RTOG classes 3 and 4, but the prospective randomized RTOG study 9305, did not confirm any survival benefit for the patients who had been treated with a radiosurgical boost as part of their upfront treatment for glioblastoma.

Hence, as also stated in an American Society for Therapeutic Radiology and Oncology (ASTRO) evidence-based review, it is now generally accepted, that radiosurgery has no additive effect when given as boost or in connection to initial standard treatment with surgical resection and fractionated radiotherapy. This is in line with other studies that failed to demonstrate a beneficial effect of a fractionated dose escalation as upfront treatment.

Surgical debulking is the mainstay of initial treatment of malignant gliomas and glioblastoma, but surgery alone is inadequate for obtaining reliable tumor control. Conventional fractionated radiation is generally applied as standard treatment of malignant glioma, but it appears that tumor recurrences are inevitable in glioblastoma. After standard fractionated radiotherapy 77%-90% patients relapsed centrally within 2 cm of the original gadolinium-enhanced mass on MRI. The virtually inevitable glioblastoma recurrence after standard treatment allows for only very few
remaining therapeutic options, since a second surgical resection is not always feasible, conventional fractionated re-irradiation is impossible and clinical benefit of chemotherapy appears to be limited. In this situation stereotactic radiosurgery has been applied. Due to the inherent limited and extremely focused radiation effect, stereotactic radiosurgery offers a potential option to treat glioblastoma recurrences in this otherwise highly critical situation.

Despite recent advances in treatment, tumor recurrence after initial therapy is inevitable and typically leads to death within a matter of months. After recurrence the remaining therapeutic options are 1. re-operation, 2. chemotherapy or 3. re-irradiation using hypo-fractionated stereotactic radiotherapy or stereotactic radiosurgery. Reoperation is a theoretical option for the treatment of recurrent glioblastoma but requires a good preoperative clinical condition. The evaluation of surgical studies is significantly impaired by the clinical bias inherently related to select patients for surgery and by the difficulties to systematically compare tumor infiltration in various anatomical tumor locations. Based on a variety of studies with rather consistent outcomes the median survival time after reoperation of recurrent glioblastoma can be estimated with 3.5 – 9 months, provided that the patients are in good preoperative clinical condition (KPS>60). FDA approved of bevacizumab for recurrent glioblastoma. In the treatment of recurrent glioblastoma with bevacizumab, the median survival after progressive disease the median overall survival was 4.5 months. Iwamoto FM, Abrey LE, Beal K, et al. Patterns of relapse and prognosis after bevacizumab failure in recurrent glioblastoma. Neurology 2009;73(15): 1200-6.

In the situation of an almost inevitable glioblastoma recurrence, the treatment is highly complex; as fractionated radiotherapy cannot be repeated and the surgical options may be limited due to the patients’ frequently reduced clinical condition. Under these circumstances stereotactic radiosurgery has been proven to be an effective alternative treatment option and patients treated at the time of progression, The reported the survival after radiosurgical treatment of the glioblastoma recurrences ranges between 6.5 and 30 months, which compares favorably to the outcome after reoperation of recurrent glioblastoma (3.5-9 months), the treatment with temozolomide and the median overall survival on bevacizumab after glioblastoma recurrence (4.5 months).
Clinical Outcome Criteria

It is important to note that survival after radiosurgery for glioma is strongly related to five selection variables (grading, age, decreased KPS, increased volume, multifocality). Much of variation in survival reported can be attributed to differences of these variables. The median survival of patients with primary glioblastoma after Gamma Knife treatment was 86 weeks if ‘brachytherapy criteria’ were satisfied. A recent prospective cohort study demonstrated that stereotactic radiosurgery with Gamma Knife or Linac significantly prolonged survival as a salvage treatment in patients with recurrent glioblastomas (23 months vs 12 months; P < .0001) when compared to a historical control group from the same institution with patients who had not been treated with radiosurgery for their recurrence. And a case-control study showed that the combination of salvage Gamma Knife radiosurgery followed by bevacizumab could add potential survival benefit and could reduce the risk of adverse radiation effects in patients with recurrent glioblastoma (33.2 months vs. 26.7 months).

Favorable outcome was reported after Gamma Knife treatment of glioblastoma recurrences were reported in a recent study from Norway by Skeie and colleagues: Median survival after Gamma Knife radiosurgery for recurrences was 12 months in 51 patients compared with 6 months in the cohort that was treated with reoperation alone (P = 0.001). The overall survival from the time of primary diagnosis was 19 months in the Gamma Knife cohort versus 16 months for the surgical patients. The complication rate was 9.8% after Gama Knife and 25.2% after reoperation.

It is intuitive that younger age and a smaller tumor volume are predictive of better outcome. In cases of recurrent glioblastoma, for the cohort of younger patients (<70) in better clinical condition (KPS >60) the survival from the date of radiosurgery was 14.3 months and 10 months when these criteria were not fulfilled. In addition, it has been demonstrated by Shrieve that patients with tumor volumes smaller than 10.1 cm³ survived longer after stereotactic radiosurgery.

Side Effects after Radiosurgery of Recurrent Glioblastoma

Side effects after the retreatment in the situation of recurrent glioblastoma are an important issue. When radiosurgery is used as salvage treatment, even this local and highly focal radiation is biologically additive to the initially applied standard fractionated radiotherapy. The occurrence of adverse
radiation effects reflects that problem. Side effects after radiosurgery are a function of irradiated volume and radiation dose. Ideally the dose should be as low as possible in a small volume to avoid adverse effects, but there might be a threshold of efficacy for the radiosurgical treatment.

Radiological adverse radiation effects were reported in 7.7% ³⁶⁹, 14%³⁶³, 23%³⁵⁸, 24%³⁶⁵, 33% ³⁷⁰, 37% ³⁷¹ and even 46% ³⁶¹, but not all adverse radiation effects that are detected in the MRI have clinical consequences. Park described adverse radiation effects in 46% in a historical control group, with 23% being clinically symptomatic ³⁶¹. Similarly, Kong observed adverse radiation effects in 24.4% of 114 patients including 49 patients with WHO III gliomas ³⁶⁵, which necessitated surgical resections in only 4 cases. Maranzano and colleagues reported adverse radiation effects in 23% that were asymptomatic and required no specific treatment ³⁵⁸.

The risk for adverse radiation effects is not necessarily related to the treatment modality but depends on the specific dose volume parameters, which are not provided in the reports. Using Gamma Knife treatments with relatively low median prescription doses of 12.2 Gy (8-20Gy), Skeie reported a series with a low risk for adverse radiation effects of 9.8%, which compared favorably with the 33.8% complication rate after open surgery ³⁶⁰. In another recent Gamma Knife studies side effects were comparably low with only 11% grade 3/4 toxicities attributable to treatment ³⁴⁰ and other observed focal radiation necrosis in 7% ³⁴⁴.

When lower doses and restricted tumor volumes are treated with radiosurgery, a low risk for side effects can be expected. In many radiosurgical series median prescription doses of 15-18Gy were applied.

**Outcome after Radiosurgical Salvage Treatment of Recurrent Glioblastoma**

In 2005 Mahajan et al. reported a case-control study of stereotactic Linac radiosurgery for recurrent glioblastoma multiforme in 41 patients ³⁶². A control group of patients who did not undergo SRS was created from an institutional database, and each case was matched for known prognostic factors in glioblastoma with control patients undergoing at least one more surgical intervention for tumor resection as part of salvage therapy. The median duration of overall survival from diagnosis was 26 months in the radiosurgically treated group and 23 months in the surgical control group. From the date of radiosurgery, the median duration of survival was 11 months in the case group and 10
months in the surgical control group, a difference that was not statistically significant. This entire patient population had longer survival duration than that reported in the literature for patients with similar prognostic factors.

In 2005 Combs et al reported 32 patients with recurrent glioblastoma multiforme who were treated with Linac radiosurgery. The median applied dose was 15 Gy (range, 10-20 Gy) prescribed to the 80% isodose line that encompassed the target volume. The median interval between primary irradiation and re-irradiation was 10 months. No concomitant chemotherapy was applied. The median overall survival from primary diagnosis of the tumor was 22 months (range, 9-133 months) and median overall survival after SRS was 10 months.

In 2005 Hsieh reported 51 consecutive patients with glioblastoma who were treated with gamma knife radiosurgery: 25 as an "upfront" adjuvant therapy after surgery or 26 at the time of tumor progression. When Gamma Knife radiosurgery was performed after the time of initial tumor resection, an overall median survival of 10 months was reached.

In 2008 Kong and colleagues treated 65 patients with recurrent glioblastoma with either Gamma Knife or Linac radiosurgery as a salvage treatment and compared these patients with a historical control group from the same institution that had been treated without radiosurgery. It was demonstrated that salvage radiosurgery significantly prolonged survival (23 months vs12 months; P <.0001). Adverse radiation effects induced by radiosurgery were observed in 24.4% (of the total population of 114 patients including 49 patients with WHO III glioma).

In 2009 Patel et al reported 26 patients with pathologically proven recurrent glioblastoma who were treated with salvage re-irradiation by Linac radiosurgery with a median dose of 18 Gy (range: 12-20 Gy). All patients had previously received radiotherapy with a dose of 50-60 Gy. The time from primary radiation to re-irradiation was 12.5 months (0.77–119) and median survival time after radiosurgery for recurrence was 8.5 months.

In 2009 Pouratian and colleagues retrospectively reviewed 26 patients with histopathological diagnoses of glioblastoma at the time of progression who had been treated with Gamma Knife radiosurgery. Patients survived a median of 9.4 months after treatment for progression. Applied radiosurgical doses were relatively low and margin dose was a significant prognostic factor on multivariate analysis. Patients treated at the time of progression had significantly longer overall survival than those treated on initial presentation (17.4 vs. 15.1 months, P = 0.003).

In 2011 Maranzano and colleagues reported 22 patients with recurrent glioblastoma who were
treated with radiosurgery or fractionated stereotactic radiotherapy, the treatment option being chosen according to lesion size and location. Median survival from re-irradiation was 11 months, 23% of patients submitted to radiosurgery developed asymptomatic brain radionecrosis \(^{358}\).

**In 2011 Elliot, Golfinos and colleagues** from the New York University Langone Medical Center, retrospectively analyzed 26 consecutive adults who underwent Gamma Knife radiosurgery for recurrent high grade gliomas (Median tumor volume 1.22 cc, median treatment dose 15 Gy) and showed a median overall survival of 13.5 months for the entire cohort from the time of Gamma Knife treatment. **Values for 12-month actuarial survival from time of Gamma Knife radiosurgery for glioblastoma multiforme (GBM; n=16), anaplastic mixed oligoastrocytoma (n=5) and anaplastic astrocytoma (n=5) were 37%, 20% and 80%.** Local failure occurred in 9 patients (37.5%) at a median time of 5.8 months, and 18 patients (75%) experienced distant progression at a median of 4.8 months. Complications included radiation necrosis in two patients and transient worsening of hemiparesis in one patient \(^{372}\).

**In a case-control study Park and colleagues** evaluated the efficacy and safety of gamma knife stereotactic radiosurgery followed by bevacizumab in 11 patients with recurrent glioblastoma in comparison to 44 case-matched controls who underwent Gamma Knife treatment without additional bevacizumab. The median tumor volume was 13.6 cm\(^3\) and the median prescription dose was 16 Gy (13-18 Gy). The patients who received bevacizumab had significantly prolonged overall survival (33.2 months vs. 26.7months, \(P = 0.048\)), and were less likely to develop an adverse radiation effect (9 vs. 46%, \(P = 0.037\)) \(^{361}\).

**In 2012 Skeie and colleagues** published a comparative retrospective study: Gamma Knife was used for recurrent glioblastoma (in 77 patients) and compared with the outcome after re-operation only: median survival after retreatment was 12 months for the 51 patients receiving GKS compared with 6 months for reoperation only (\(P = 0.001\)), and median survival was 19 months versus 16 months from the time of primary diagnosis (\(P = 0.021\)). The study showed significantly longer survival for patients treated with Gamma Knife, both from retreatment (\(P = 0.013\)) and from primary diagnosis (\(P = 0.002\)). The adjusted results were still significant after separate analysis according to tumor volumes <5 mL, 5 to 20 mL, and >20 mL. The complications rate was 9.8% after GKS and 25.2% after re-operation \(^{360}\).

**In 2014 Dodoo, Lippitz and colleagues** assessed gamma knife radiosurgery in the management of high-grade glioma recurrences in 55 consecutive patients with WHO III and WHO IV glioma. All patients had undergone previous microsurgery and radiochemotherapy (median follow-up 17.2
months; 2.5-114.2 months; median tumor volume 5.2 cm³, median prescription dose 20 Gy; 14-22 Gy), The patients with WHO III tumors showed a median survival of 49.6 months with and a 2-year survival of 90%. After Gamma Knife radiosurgery of the recurrent tumors, these patients showed a median survival of 24.2 months and a 2-year survival of 50%. The patients with WHO IV tumors had a median survival of 24.5 months with a 2-year survival of 51.4%. After the recurrence was treated with Gamma Knife radiosurgery, the median survival was 11.3 months and a 2-year survival: 22.9% for the WHO IV patients.

In 2015 Niranjan, Lunsford and colleagues performed Gamma Knife SRS in 297 patients with histologically proven glioblastomas (median tumor volume 14 cm³; range 0.26-84.2 cm³; median prescription dose 15 Gy; range 9-25 Gy). All patients had received prior fractionated radiation therapy, and 66% had undergone one or more chemotherapy regimens. Radiosurgery at the time of tumor progression was associated with a median survival of 21.8 months.

In conclusion, salvage stereotactic radiosurgery can be applied in the treatment of glioblastoma recurrences. In the vast majority of studies the overall median survival ranged between 18 and 33.2 months, which is more favorable than the outcome in the best prognostic group of glioblastoma patients (RPA class 3) after conventional treatment. In the salvage situation the median survival was 10-30 months after radiosurgery of the recurrence, which compares favorably to the outcome after reoperation of recurrent glioblastoma (3.5-9 months), the treatment with temozolomide and the median overall survival on bevacizumab after glioblastoma recurrence (4.5 months). For patients with recurrent glioblastoma the outcome after use of stereotactic radiosurgery appeared to be at least equivalent to repeated surgical resection and more effective than chemotherapy alone. Hence the retrospective evidence shows that stereotactic salvage radiosurgery in general and Gamma Knife radiosurgery in particular offers a safe and effective minimal invasive treatment strategy for glioblastoma recurrences in a situation when only very few alternative options exist.

Table 2: Radiosurgery as salvage treatment of recurrent glioblastoma:

(Series where radiosurgery was used for different cohorts for primary treatment and for recurrences may appear as separate groups in table 1 and 3: ... When series contain cohorts of patients treated with various modalities, the number of radiosurgically treated patients is given in the table (i)
<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Type of Study</th>
<th>Radiosurgery Method</th>
<th>Median Age (years)</th>
<th>Median Prescription Dose</th>
<th>Number of Patients</th>
<th>Complication Rate (grade III or IV toxicity)</th>
<th>Median Survival After Retreatment (months)</th>
<th>Overall Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeie BS et al.</td>
<td>1996-2007</td>
<td>Comparative retrospective</td>
<td>Gamma Knife</td>
<td>55.3 (27-73)</td>
<td>2.2 Gy (3-20 Gy)</td>
<td>77</td>
<td>ARE in 9.8%</td>
<td>2 mo</td>
<td>19 mo</td>
</tr>
<tr>
<td>Park Ki et al.</td>
<td>2012</td>
<td>Case-control study</td>
<td>Gamma Knife without bevacizumab</td>
<td>64 (41-77)</td>
<td>5 Gy (0-20)</td>
<td>80</td>
<td>46% (ARE)</td>
<td>2.2 mo</td>
<td>26.7 mo (21.8-31.6)</td>
</tr>
<tr>
<td>Park Ki et al.</td>
<td>2007-2010</td>
<td>Case-control study</td>
<td>Gamma Knife with bevacizumab</td>
<td>62 (46-72)</td>
<td>6 Gy (3-18)</td>
<td>11</td>
<td>9%</td>
<td>7.9 mo</td>
<td>33.2 mo (23.7-42.7)</td>
</tr>
<tr>
<td>Pouratian N et al.</td>
<td>2009</td>
<td>Retrospective</td>
<td>Gamma Knife</td>
<td>60.1 (12.9-76.9)</td>
<td>6 Gy (3-15)</td>
<td>26</td>
<td>No recorded radiation necrosis</td>
<td>9.4 mo (7.9-10.9)</td>
<td>17.4 mo (14.4-20.4)</td>
</tr>
<tr>
<td>Kong DS et al.</td>
<td>2008</td>
<td>Prospective cohort study</td>
<td>Gamma Knife and Linac</td>
<td>49 (5-75)</td>
<td>16 Gy (12-50 Gy)</td>
<td>65</td>
<td>24.4% radionecrosis</td>
<td>13 mo (10.6-16.0)</td>
<td>23.0 mo (16.2-29.3)</td>
</tr>
<tr>
<td>Hsieh PC et al.</td>
<td>2005</td>
<td>Retrospective</td>
<td>Gamma Knife</td>
<td>59 (17-81)</td>
<td>120 Gy</td>
<td>26</td>
<td>33% radionecrosis (17/51)</td>
<td>16.7 mo</td>
<td></td>
</tr>
<tr>
<td>Wendt D et al.</td>
<td>1997</td>
<td>Retrospective</td>
<td>Gamma Knife</td>
<td>51 (3-72)</td>
<td>15.5 Gy (12-25 Gy)</td>
<td>19</td>
<td>GBM recurrences</td>
<td>30 mo (2-74)</td>
<td>MST Not specified For recurrent GBM</td>
</tr>
<tr>
<td>Larson DA et al.</td>
<td>1996-1994</td>
<td>Retrospective</td>
<td>Gamma Knife</td>
<td>Not specified for GBM</td>
<td>16 Gy (5-37.5)</td>
<td>66</td>
<td>GBM recurrences</td>
<td>Not mentioned</td>
<td>Median overall survival not specified for recurrent GBM</td>
</tr>
</tbody>
</table>

**Arterio-venous malformations (AVM)**

An arterio-venous malformation (AVM) in the brain is a vascular anomaly resulting in a direct shunt
between arteries and veins. The absence of capillaries creates a lack of resistance and hence a short-cut for blood to pass directly from arteries to veins. The result is a risk for a bleeding within the brain potentially resulting in neurological deficits or even death. Other patients with AVMs of the brain may experience epileptic seizures or other neurological symptoms even without a bleeding.

The overall detection rate of symptomatic AVM appears to be 0.94 per 100,000 person-years (95% confidence interval, 0.57-1.30/100,000 person-years). The prevalence of detected, active (at risk) AVM disease is unknown, but it can be inferred from incidence data to be lower than 10.3 per 100,000 population.

In general, AVMs are associated with a 2 to 4% annual hemorrhage risk. A deep location for AVMs is a risk factor for neurological deficit for any possible treatment and is known to be a higher risk for neurological deficit in case of a hemorrhage. Often deeply seated AVMs are considered inoperable. According to the natural history of AVMs in the basal ganglia or thalamus and showed that 72% of the patients presented with an intracranial hemorrhage and 86% of patients who had experienced a hemorrhage, suffered either from hemiparesis or hemiplegia.

Patients with aneurysms within the nidus of the AVM, intranidal aneurysms, presented more frequently with hemorrhage (72% compared with 40%, p < 0.001) and had a significantly increased risk of bleeding, with a rate of 9.8% per year. Hence, patients with aneurysms and an AVM warrant more aggressive surgical or endovascular treatment to reduce the risk of a hemorrhage in the latency period after SRS. In addition, a venous stenosis increases the risk for hemorrhage.

When possible, AVMs are removed to prevent a cerebra hemorrhage. The removal can be achieved through a classical neurosurgical operation under the microscope. As an alternative it is sometimes possible to reduce the volume of the AVM or its blood flow using an intravascular approach, through embolization, when the pathological arterio-venous shunts are occluded using highly selective catheters. Unfortunately only in exceptions the endovascular approach achieves a complete occlusion of the AVM.

An increasingly important alternative is the AVM treatment with Gamma Knife radiosurgery. Until 2014 more than 103,000 AVM treatments have been carried out using Gamma Knife radiosurgery.
and the results are well documented. The AVM is localized with both angiography and MRI and then treated with focal Gamma Knife radiation. The result is an irritation of the vessel wall that slowly occludes the pathological vessels of the AVM.\textsuperscript{381}

The latency between Gamma Knife Radiosurgery and obliteration is dose dependent. In general it is assumed that the obliteration process takes 2-3 years. This occlusion generally prevents potential future bleedings and the patient is considered cured.\textsuperscript{379}

In a typical large of series 400 patients with AVM treated with Gamma Knife radiosurgery it was shown that at 3 years after treatment 72\% of treated AVMs were obliterated and 87.3\% at 5 years.\textsuperscript{382} The obliteration rate increases with increasing prescription dose applied to the nidus periphery with statistically significant correlation between outcome and dose prescribed to the margin.\textsuperscript{383-387}

Factors leading to a better obliteration rate were: previous hemorrhage ($p = 0.0084$), smaller nidus ($p = 0.0023$), higher radiation dose to the lesion's margin ($p = 0.0495$) and factors leading to an earlier obliteration of the nidus were: male sex ($p = 0.0001$), previous hemorrhage ($p = 0.0039$), smaller nidus diameter ($p = 0.0006$).\textsuperscript{382}

The incidence of adverse radiation effects is related to the volume of the 12 Gy isodose volume and hence related to the size of the AVM, but the risks of developing permanent symptomatic sequelae from AVM radiosurgery vary dramatically with location and, to a lesser extent, volume.\textsuperscript{388}

In general, reasons for treatment failures can be: 1. insufficient definition of Nidus due to suboptimal imaging technique resulting in incomplete coverage of the AVM, 2. reexpansion after hematoma reabsorption, 3. failure to fill part of the nidus as a result of hemodynamic factors and 4. recanalization after embolization. Sometimes suboptimal radiation dose ($<20\text{ Gy}$) in larger AVM volumes or in eloquent area can result in lower obliteration rates. In some patients the AVM has been shown to fail to obliterate despite correct target definition and adequate dose.\textsuperscript{389}

Regrowth of an AVM with subsequent hemorrhage has been documented in children and is attributed to forces acting on the immature vasculature.\textsuperscript{390,391}
Treatment Doses (AVM)

In an initial attempt to define effective radiosurgical doses in the treatment of AVM, Flickinger, Lunsford and associates analyzed the results of radiosurgery in 197 AVM patients with 3-year angiographic follow-up revealing a complete AVM obliteration in 72%. Multivariate logistic regression analysis of in-field obliteration revealed a significant independent correlation with the minimum target dose (p = 0.04), but not with volume or maximum dose. A sigmoid dose-response curve for in-field obliteration was constructed. In a recent review (2013) Flickinger confirmed the previous results by stating that the dose response of stereotactic radiosurgery of AVM is relatively steep between 12 and 17 Gy, while leveling out at around 20 Gy. Even at low doses of 14Gy the chance of obliteration is in the range of 50%.

While prescription doses > 20 Gy are generally considered effective for an obliteration, Inoue published a series of 114 patients with AVMs who had been treated with Gamma Knife at lower prescription doses of 20-Gy or less (mean margin dose 19.5 Gy) and demonstrated a total angiographically documented obliteration in 85.5%. Symptomatic edema was seen in only 1.7%. In two pediatric cohorts, AVM obliteration was achieved in 52% of patients who received a dose of 18-20 Gy and in 16% who received less than 18 Gy.

Surprisingly, in 363 pediatric patients Dinca, Kemeny and colleagues found no correlation between outcome and radiosurgical dose when that dose was between 20 and 25 Gy, thus suggesting that even the lower of these 2 doses may be effective.
Dose response curves for AVM obliteration according to prescription dose and history of prior embolization from 515 patients with >5 years of follow-up. Logistic model, $\alpha/\beta = -45.9$; maximum obliteration at 23 Gy; 95.7% with no embolization, 91.8% with prior embolization. From: Flickinger et al. \(^{386}\)

**Clinical Relevance of Technical Development**

The outcomes for 492 patients (564 treatments) with large AVMs >10 cm\(^3\) treated by single-stage Gamma Knife radiosurgery were retrospectively analyzed by the team from the Royal Hallamshire Hospital, Sheffield, UK. Twenty-eight percent of the patients presented with haemorrhage at a median age of 29 years (range: 2-75). From 1986 to 1993 (157 patients) plans were simplistic, based on angiography using a median of 2 isocenters and a marginal dose of 23 Gy covering 45-70% of the AVM (median volume 15.7 cm\(^3\)). From 1994 to 2000 (225 patients) plans became more sophisticated, a median of 5 isocenters was used, covering 64-95% of the AVM (14.6 cm\(^3\)), with a marginal dose of 21 Gy. Since 2000, MRI has been used with angiography to plan for 182 patients. Median isocenters increased to 7 with similar coverage (62-94%) of the AVM (14.3 cm\(^3\)) and marginal dose of 21 Gy. **Excluding the embolized patients, improvement in planning increased obliteration rates from 28% to 36% and finally 63%**. Improving treatment plans did not significantly decrease the rate of persisting radiation-induced side effects (12-16.5%). Complication rate rose with increasing treatment volume. One hundred and twenty-three patients underwent a second radiosurgical treatment, with a 64% obliteration rate, and mild and rare complications in 6% \(^{395}\).
General Obliteration Rate in AVM

In 2007 Liscak and associates summarized the results after gamma knife radiosurgery in 330 patients with AVMs (median volume 3.9 cm³; range 0.15 to 28.6 cm³). When complete obliteration was not achieved within 3 years, repeat radiosurgery was performed on 76 patients. AVM obliteration was achieved in 74% patients after the first round of radiosurgery and in 47 (69%) after the second. The overall chance of cure was 92% (269 patients). Final angiography verified complete obliteration by 12 to 96 months (median, 25 mo) after initial radiosurgery. The risk of rebleeding after radiosurgery was 2.1% annually until full obliteration, and the overall mortality from rebleeding was 1%. The risk of permanent morbidity after the first and second radiosurgery treatments were 2.7 and 2.9%, respectively.

Very similar results with obliteration rates of 72% at 3 years and 87.3% at 5 years had been shown in 400 patients with AVM treated with Gamma Knife at the University of Tokyo as published by Shin, Kirino and associates.

Previously Pollock and colleagues had reported excellent outcomes (obliteration without deficit) in 66.7% and good outcomes (obliteration with minor deficit) in 6.25% of 144 patients after one or more radiosurgical procedures. In this series 10.4% of patients sustained major deficits and 3.5% died.

In 2008 Douglas and Goodkin summarized the outcome of 95 patients with 99 treatable AVMs after Gamma Knife treatment at the University of Washington (median AVM volume 3.8 cm³; range 0.12-32 cm³, median prescription dose 20 Gy; median follow-up 38 months; range 3-91 months). The Kaplan-Meier estimated 6-year AVM obliteration rate for the entire cohort was 71.4%. The median time to AVM obliteration was 47 months, 7.4% experienced late toxicities. There were 2 fatal bleeds and 13.8% nonfatal bleeds after Gamma Knife surgery.

In 2014 Paúl, Martinez and associates published a retrospective, longitudinal study of 662 consecutive patients with brain AVMs treated with Gamma Knife brain AVMs at the Ruber International Hospital, Madrid (median AVM volume 3.6 cm³; mean follow-up 11 years). The obliteration rate after a single RS was 69.3%; after multiple RS, it was 75%. Positive predictors of
obliteration included compact nidus, undilated feeders, smaller AVM volume, and higher marginal dose \(^{399}\)

In a large retrospective study comprising 774 patients, it was demonstrated that non-smokers were more likely to have obliterated AVMs through radiosurgery. Smoking was not predictive of treatment complications or post-treatment hemorrhage. In a multivariate analysis a negative smoking history (OR 1.9, \(p = 0.006\)) was a strong independent predictor of AVM obliteration. Of the patients with obliterated AVMs, 31.9% were smokers, whereas 45% were not (\(p = 0.05\)) \(^{400}\).

In 2014 Paúl, Martinez and associates published a retrospective, longitudinal study of 662 consecutive patients with brain AVMs treated with Gamma Knife brain AVMs at the Ruber International Hospital, Madrid (median AVM volume 3.6 cm\(^3\); mean follow-up 11 years). The obliteration rate after a single RS was 69.3%; after multiple RS, it was 75%. Positive predictors of obliteration included compact nidus, undilated feeders, smaller AVM volume, and higher marginal dose \(^{399}\).

In a series of 102 patients patients treated for an AVM with single-dose or staged-dose Gamma Knife stereotactic radiosurgery, overall nidus obliteration was achieved in 75% of patients. Morbidity (19%) correlated with lesion size and Spetzler-Martin grade. For Spetzler-Martin Grade I-III AVMs, treatment yielded obliteration rates of 100%, 89%, and 86%, respectively and 1% mortality. For Spetzler-Martin Grade IV and V AVMs, outcomes were less favorable, with obliteration rates of 54% and 0%, respectively \(^{401}\).

Starke, Sheehan and associates proposed a grading scale to predict the long-term outcome of radiosurgically treated AVM patients based on 1012 patients who had been followed-up for more than 2 years. Obliteration had occurred in 69% of patients, post-radiosurgery hemorrhage occurred with a yearly incidence of 1.14%, radiation-induced changes 38.2%, symptoms in 9.9%, and permanent deficits in 2.1% \(^{402}\).

The Virginia Radiosurgery AVM Scale assigned 1 point each for having an AVM volume of 2-4 cm\(^3\), eloquent AVM location, or a history of hemorrhage, and 2 points for having an AVM volume greater than 4 cm\(^3\). Eighty percent of patients who had a score of 0-1 points had AVM obliteration and no
post-treatment hemorrhage, as did 70% who had a score of 2 points and 45% who had a score of 3-4 points.

**Side Effects (AVM)**

An early essential study by Flickinger, Lunsford and colleagues had established that the 12 Gy volume was the only independent variable that correlated significantly with post-radiosurgical imaging changes (p < 0.0001), while symptomatic post-radiosurgical imaging changes were correlated with both 12 Gy volume (p = 0.0013) and AVM location (p = 0.0066). In this series of 307 AVM patients who received gamma knife radiosurgery at the University of Pittsburgh between 1987 and 1993 the 7-year actuarial rate for developing persistent symptomatic post-radiosurgical imaging changes was 5.05%. Recently Hayhurst, Zadeh and colleagues confirmed these results and found in 125 patients with radiosurgically treated AVM that target volume and 12 Gy volume were the most significant predictors of adverse radiation effects on univariate analysis (p < 0.001) with a significant target volume threshold of 4 cm³, above which the rate of adverse radiation effects increased significantly.

Radiation-induced imaging changes are newly developed increased T2 signal surrounding the treated AVM nidi are seen considerably more frequently than clinical side effects: in a large series of 1426 Gamma Knife procedures for AVMs from the University of Virginia, Charlottesville, radiation-induced imaging changes were seen in 33.8% of treated AVM at a median latency of 13 months (range 2-124 months). After a median of 22 months the imaging changes disappeared completely (range 2-128 months). The overall incidence of symptomatic imaging changes was 8.6% and 1.8% had permanent deficits. Similarly, in a subgroup of 140 patients treated with repeat Gamma Knife at the University of Virginia, Charlottesville, radiation-induced changes were visualized on magnetic resonance imaging in 39%, while only 3.6% of patients developed permanent neurological deficits.

Hypertension, patient sex, tobacco use, number of draining veins, superficial or deep location of the lesion, and AVM embolization prior to radiosurgery had no association with the presence of radiation-induced changes. According to a multivariate analysis, larger AVM volume, worse Spetzler-Martin grade, and no AVM surgery prior to radiosurgery predicted the occurrence of
radiation-induced changes. Diabetes mellitus had borderline significance \(^{406}\).

In general, there is a low risk of side effects after Gamma Knife radiosurgery of AVM. Clinical side effects have been reported in 1.5\(^{407}\), 2.3\(^{379}\), 3.2\%-3.6\% (in children) \(^{394,408}\), 3.6\% \(^{389}\) and 4.5\% in AVMs of the basal ganglia and thalamus \(^{409}\) and 6\% in Spetzler-Martin Grade III AVM \(^{410}\).

During a mean long-term follow-up period of 10.2 years (range, 5.4-30.6) in 181 consecutive patients who underwent Gamma Knife radiosurgery for AVM, 8.3\% experienced stereotactic radiosurgery-related, symptomatic complications. Among these 15 patients, 12 manifested complications 5 years or more after Gamma Knife \(^{411}\).

A higher rate of long-term side-effects in 9.3\%, occurring 2 or more years after gamma knife surgery, was observed by Izawa, Takakura and colleagues in 2005. The complications included hemorrhage (n=8), delayed cyst formation (n=8), increase of seizure frequency (n=4), and middle cerebral artery stenosis (n=1) and increased white matter signal intensity on T2-weighted magnetic resonance imaging (n=1). The long-term complications were associated with larger nidus volume (p < 0.001) and a lobar location of the AVM (p < 0.01). Delayed cyst formation was associated with a higher maximal GKS dose (p < 0.001), larger nidus volume (p < 0.001), complete nidus obliteration (p < 0.01), and a lobar location of the AVM (p < 0.05). Out of 237 cases in this series, complete AVM obliteration was attained in 54.9\% \(^{412}\).

In highly eloquent anatomical regions such as the brainstem permanent neurological deficits due to adverse radiation effects developed in 10\% \(^{413}\).

Also in larger AVM the risk for symptomatic adverse radiation is known to be higher, which is a clear limitation of stereotactic radiosurgery. Volume staged treatments are carried out in order to reduce these potential side effects. **Symptomatic adverse radiation were detected after volume-staged Gamma Knife radiosurgery of larger AVM in 13\% of patients \(^{414}\) and after repeat radiosurgery in 9.5\% \(^{415}\).**
Gamma Knife treatment of AVMs Spetzler-Martin Grade III

Based on the functional eloquence of the affected surrounding brain, the size of the AVM and the type of venous drainage, cerebral AVMs are categorized according to Spetzler-Martin Grades. Spetzler-Martin Grading allows the prediction of potential side effects associated with a surgical resection of the AVM. The impact of this grading system cannot be directly translated into radiosurgical indications, but AVMs that are classified according to Spetzler-Martin Grades Grade III can be very difficult to remove surgically due to a high risk of potential side effects.

Over the 20-year span from 1989 to 2009 a total of 398 patients with Spetzler-Martin Grade III AVMs were treated with stereotactic Gamma Knife radiosurgery at the University of Virginia (median AVM volume 2.8 cm$^3$, median prescription dose 20 Gy; median radiological follow-up intervals 54 months). Complete AVM obliteration was observed in 69% of Grade III AVM cases at a median time of 46 months after radiosurgery with actuarial obliteration rates at 3 and 5 years were 38% and 60%, respectively. The obliteration rate was higher in ruptured AVMs than in unruptured ones ($p < 0.001$) and in cases with a single draining vein ($p = 0.018$). The annual risk of postradiosurgery hemorrhage during the latency period was 1.7%. The rates of symptomatic and permanent radiation-induced imaging changes were 12% and 4%, respectively $^{416}$.

The corresponding series from Pittsburgh comprised 474 patients with Spetzler-Martin Grade III AVM (median target volume 3.8 ml; range 0.1-26.3 ml; prescription dose 20 Gy; range 13-25 Gy) showed virtually identical results: At a mean follow-up of 89 months, the total obliteration rates documented by angiography or MRI increased from 48% at 3 years to 69% at 4 years, 72% at 5 years, and 77% at 10 years. The cumulative rate of hemorrhage was 2.3% at 1 year, 4.4% at 2 years, 5.5% at 3 years, 6.4% at 5 years, and 9% at 10 years $^{410}$. Symptomatic adverse radiation effects were detected in 6%.

The consequence is that Gamma Knife radiosurgery can be considered as a safe treatment alternative in these otherwise very complex and often inoperable AVMs.
**Gamma Knife treatment for AVM Spetzler-Martin Grade I or II**

Patients with AVMs classified according to Spetzler-Martin Grade I or II are generally considered as operable. In these cases surgery is generally considered as treatment of choice, since the bleeding risk disappears immediately with successful surgery and a resection can generally be carried out at a limited risk for surgical side effects.

However, under specific circumstances surgery is not always possible and Gamma Knife radiosurgery is an effective and relatively safe option for patients with smaller volume Spetzler-Martin Grade I or II AVMs who decline initial resection.  

Kano, Kondziolka and the team from the University of Pittsburgh analyzed the outcome for Gamma Knife radiosurgery of AVM classified according to Spetzler-Martin Grade I and II in 217 patients (median target volumes 2.3 cm$^3$; range 0.1-14.1 cm$^3$; median margin dose 22 Gy; range 15-27 Gy). The actuarial rates of total obliteration determined by angiography or MR imaging after 1 Gamma Knife procedure were 58%, 87%, 90%, and 93% at 3, 4, 5, and 10 years, respectively. The median time to complete MR imaging-determined obliteration was 30 months. Factors associated with higher AVM obliteration rates were smaller AVM target volume, smaller maximum diameter, and greater marginal dose. The annual bleeding risk was 3.7%, 0.3%, and 0.2% for Years 0-1, 1-5, and 5-10, respectively, after radiosurgery. The presence of a coexisting aneurysm proximal to the AVM correlated with a significantly higher hemorrhage risk. Temporary symptomatic adverse radiation effects developed in 2.3% after SRS, and 1% developed delayed cysts.

**Dural Arteriovenous Fistulas**

So far treatment options and management strategies for dural arterio-venous fistulas are ranging from observation to surgical excision to endovascular embolization and radiosurgery. Niranjan and Lunsford made an attempt to formulate guidelines about the use of radiosurgery in symptomatic patients with imaging-identified dural arterio-venous fistulas of the brain and concluded that Gamma Knife treatment before embolization facilitates the better recognition of the entire target. For selected dural arterio-venous fistulas patients who are not eligible for embolization or surgery, radiosurgery alone is an effective treatment option. The dose range for dural arterio-venous fistulas is similar to that of arterio-venous malformations. A total of 40 patients with dural arterio-
venous fistulas underwent Gamma Knife treatment at the University of Pittsburgh (median target volume 2.0 cm³, median marginal dose 21.0 Gy). The obliteration rate was 83% for patients who had upfront SRS and embolization. The obliteration rate was lower (67%) for patients managed with SRS alone.\textsuperscript{418}

Of 22 patients who underwent Gamma Knife surgery for the management of dural arteriovenous fistulas at the University of Tokyo Hospital, 55% had an obliteration. The obliteration rate for lesions without cortical venous drainage was 86% and thus significantly higher than in fistulas with cortical venous drainage (47%) (\(p = 0.007\)). Hemorrhage at presentation (\(p = 0.03\)), a target volume less than 1.5 cm³ (\(p = 0.009\)), and Cognard Type III or IV dAVF (\(p = 0.005\)) were factors associated with a higher obliteration rate.\textsuperscript{419}

During the period between 1972 and 2008, 65 consecutive patients with dural arteriovenous fistulae were treated and followed-up at the Karolinska Hospital Stockholm. Prescription doses varied considerably, but most commonly it was 20-25 Gy to the 40-60% isodose. There were 59% obliterations, 2 post-treatment hemorrhages and 5 minor adverse radiation effects.\textsuperscript{420}

In 2013 Pan, Guo and associates presented an update on 321 patients with dural arteriovenous fistulas (DAVF) treated at the Taipei Veterans General Hospital using Gamma Knife radiosurgery. The prescribed mean margin dose was 17.2 Gy. For the cavernous sinus DAVFs, 70% showed complete improvement. For the non-cavernous- sinus DAVFs, 59% showed complete improvement. The results show that radiosurgery was effective in treating Borden type I lesions with a 72% complete obliteration rate. However, for Borden type II and III lesions, a lower cure rate was observed with complete obliteration in 44%\textsuperscript{421}. In this series, 98% of patients had a stable or improved clinical condition after radiosurgery.

**Effect of Gamma Knife on Seizure Activity in AVM Patients**

Yang, Paek and colleagues reviewed a series of 86 patients with a history of seizure who underwent stereotactic radiosurgery for unruptured cerebral AVM with a mean follow-up of 89.8 months showing that \textbf{76.7% were seizure-free and 58.1% were medication-free at the last follow-up visit. Of the patients who achieved AVM obliteration, 96.7% (58/60) were seizure-free} while 30.8%
(8/26) of those patients who did not achieve AVM obliteration were seizure-free \( (p = 0.001) \). Of the 75 patients with no history of seizure before radiosurgery, 10 had provoked seizures due to the direct and indirect radiosurgical influences after radiosurgery 422.

Similarly Lim, Rhee and colleagues found after Gamma Knife radiosurgery for AVMs in patients who had presented with seizures \((n=45)\), that **84.6% of patients with complete obliteration were seizure-free**. In total 53.5% became seizure-free, 23.3% had significant improvement, 18.6% were unchanged and 4.6% were aggravated 423.

**Pediatric AVM**

In a comparison between pediatric and adult patients with AVM, Pan, Wong and associates from the Taipei Veterans General Hospital found in 2008 that AVMs between 3 and 10 cm³ responded less efficaciously in children \( (p = 0.042) \), while obliteration rates of small and extremely large \((> 20\, \text{cm}^3)\) AVMs were similar in the pediatric and adult groups 424.

This team had summarized their data after Gamma Knife surgery for cerebral AVM in 105 pediatric patients \((< 18\, \text{years of age})\) and compared the outcome with the results in 458 adult patients with AVMs: **in pediatric patients, the AVM obliteration rate at 48 months after a primary GKS was 65%**. **The efficacy of GKS correlated with the size of the AVM: 91% for small, 86% for medium, and 64% for large AVMs** 424. The treatments were associated with an 8% morbidity rate and < 1% mortality rate. Post-treatment hemorrhage occurred in 4% 424.

At the National Centre for Stereotactic Radiosurgery, Royal Hallamshire Hospital, Sheffield, 363 pediatric patients \((\text{ages 1-16 years})\) underwent Gamma Knife surgery \((\text{mean lesion volume } 3.75 \pm 5.3\, \text{cm}^3; \text{range } 0.01-32.8\, \text{cm}^3; \text{mean prescription dose was } 22.7 \pm 2.3\, \text{Gy}; \text{range } 15-25\, \text{Gy})\). The most common presenting symptoms had been: hemorrhage \((80.2\%)\), epilepsy \((8.3\%; \text{overall seizure prevalence } 19.9\%)\), and migrainous headaches \((6.3\%).\) Only 0.28% of the AVMs were incidental findings. **The overall obliteration rate was 82.7%** and was 71.3% in patients who received one treatment and 62.5% for retreated patients, with a mean obliteration time of 32.4 and 79.6 months, respectively. The bleeding rate post-radiosurgery was 2.2%, and the cumulative complication rate was 3.6% 394.
In 2010 Yen, Sheehan and associates reviewed 186 patients with AVMs who were 18 years of age or younger were treated with Gamma Knife radiosurgery at the University of Virginia (mean nidus volume 3.2 cm$^3$, mean prescription dose 21.9 Gy). After initial GKS, 49.5% of patients achieved total angiographic obliteration. The obliteration rate increased to 58.6% after a second or multiple GKS. The hemorrhage rate was 5.4% within 2 years after GKS and 0.8% between 2 and 5 years. Six patients developed neurological deficits along with the radiation-induced changes. Two patients developed asymptomatic meningiomas 10 and 12 years after GKS. After a mean clinical follow-up of 98 months, less than 4% of patients had difficulty attending school or developing a career.

In another large retrospective analysis Kano, Lunsford and associates from the University of Pittsburgh reviewed the outcome of 135 pediatric patients with cerebral AVM after Gamma Knife surgery (median maximum diameter 2.0 cm; range 0.6-5.2 cm; median target volumes 2.5 cm$^3$; range 0.1-17.5 cm$^3$, median margin dose 20 Gy; range 15-25 Gy). The actuarial rates of total obliteration documented by angiography or MR imaging were 45%, 64%, 67%, and 72% at 3, 4, 5, and 10 years, respectively. The median time to complete angiographically documented obliteration was 48.9 months. Factors associated with a higher rate of documented AVM obliteration were smaller AVM target volume, smaller maximum diameter, and larger margin dose. In 6% a hemorrhage occurred during the latency interval, and 1 patient died. The rates of AVM hemorrhage after SRS were 0%, 1.6%, 2.4%, 5.5%, and 10.0% at 1, 2, 3, 5, and 10 years, respectively. The overall annual hemorrhage rate was 1.8%. Permanent neurological deficits due to adverse radiation effects developed in 1.5% after SRS, and in 0.7% delayed cyst formation occurred.

In 2014 Potts, Gupta and associates published a retrospective review of 2 cohorts of 80 children with AVMs treated from 1991 to 1998 and from 2000 to 2010 (median target volume 3.1 cm$^3$; range 0.09-62.3 cm$^3$, median prescription dose 17.5 Gy; range 12-20 Gy). AVM obliteration was achieved in 52% of patients who received a dose of 18-20 Gy and in 16% who received less than 18 Gy. At 5 years after SRS, the cumulative incidence of hemorrhage was 25%. No permanent neurological deficits occurred in patients who did not experience post-treatment hemorrhage.

In another series of children with arteriovenous malformations who had been treated with Gamma Knife radiosurgery at the Gazi University, Ankara (median AVM volume 3.5 cm$^3$), complete AVM
Obliteration was achieved in 68.9%, while 15.51% of the patients experienced new deficits and 5.1% experienced intracranial hemorrhage. In a series from Tokyo Women's Medical University, 22 children underwent GKS for AVMs (prescribed isodose volume < 4.0 cm³, median prescription dose 22 Gy; range 20-25 Gy). If the volume of the nidus was larger than 4.0 cm³, a second radiosurgical session was planned for 3-4 years after the first one. Complete obliteration of the AVM was noted in 77% within a median period of 47 months after the last radiosurgical session. Complete obliteration of the lesion occurred in 89% of patients after unstaged treatment and in 62.5% after staged GKS. Complications included 3 bleeding episodes.

Unruptured cerebral arterio-venous malformations in pediatric patients (age <18 years) had been excluded from ‘A Randomized Trial of Unruptured AVMs’ (ARUBA). Ding, Sheehan and colleagues analyzed the outcome in 51 unruptured pediatric AVM patients who had been treated with Gamma Knife radiosurgery (median nidus volume 3.2 cm³; radiosurgical margin dose 21.5 Gy; median radiologic follow-up 45 months). The actuarial AVM obliteration rates at 3, 5, and 10 years were 29 %, 54 %, and 72 %, respectively. Obliteration rates were significantly higher with a margin dose of at least 22 Gy and for nidi with 2 or fewer draining veins. The incidences of radiologically evident, symptomatic, and permanent radiation-induced changes were 55 %, 16 %, and 2 %, respectively. The annual post-radiosurgery hemorrhage rate was 1.3 %, and the incidence of post-radiosurgery cyst formation was 2 %.

Thalamic/Basal Ganglia and Brainstem AVM

Nagy, Kemeny and associates conducted a retrospective analysis of 356 thalamic/basal ganglia and 160 brainstem AVMs treated with gamma knife radiosurgery. Median volume was 2cm³; (range 0.02-50) for supra-tentorial and 0.5cm³ (0.01-40) for brainstem AVMs; the marginal treatment doses were 17.5-25Gy. After single treatment, obliteration was achieved in 65% of the brainstem, in 69% of the supra-tentorial, and 40% of the peri-tectal AVMs. Complications were rare (6-15%) and mild (≤MRS2). Rebleed rate increased with size, but was not higher than before treatment. AVMs >4cm in the brainstem were treated with unacceptable morbidity and low cure rate.

In 2012 Kano, Lunsford and colleagues from the University of Pittsburgh reviewed the outcome of 133 patients in centrally located AVM: 56 patients who had been treated with Gamma Knife surgery
had AVMs of the basal ganglia and 77 had AVMs of the thalamus (median target volume 2.7 cm³; range 0.1-20.7 cm³; median margin dose 20 Gy, range 15-25 Gy). The actuarial rates of total obliteration after radiosurgery were 57%, 70%, 72%, and 72% at 3, 4, 5, and 10 years, respectively. Factors associated with a higher rate of AVM obliteration included AVMs located in the basal ganglia, a smaller target volume, a smaller maximum diameter, and a higher margin dose. Eleven percent (of 133 patients) suffered a hemorrhage during the latency period and 7 patients died. The rate of post-SRS AVM hemorrhage was 4.5%, 6.2%, 9.0%, 11.2%, and 15.4% at 1, 2, 3, 5, and 10 years, respectively. The overall annual hemorrhage rate was 4.7%. Permanent neurological deficits due to adverse radiation effects developed in 4.5%, and in 1 patient a delayed cyst developed 56 months after SRS.

In 67 patients had brainstem AVMs treated by the same group (median target volume 1.4 cm³; range 0.1-13.4 cm³; median margin dose 20 Gy; range 14-25.6 Gy) showed actuarial rates of total obliteration were 41%, 70%, 70%, and 76% at 3, 4, 5, and 10 years, respectively with AVM hemorrhage after SRS in 3.0%, 3.0%, and 5.8% at 1, 5, and 10 years, respectively. The overall annual hemorrhage rate was 1.9%. Permanent neurological deficits due to adverse radiation effects developed in 10% after SRS, and a delayed cyst developed in 3%. Higher 12-Gy volumes and higher Spetzler-Martin grades were associated with a higher risk of symptomatic AREs.

In 2009 Kiran, Mahapatra et al. had studied the outcome of 53 patients with central AVMs in basal ganglia, thalamus and brainstem (central/deep) treated with Gamma knife radiosurgery at the Neuro Sciences Centre, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India (mean marginal dose 23.3 Gy; range 16-25 Gy; mean follow-up was 28 months (range 12-96 months) and published a complete obliteration of the AVM was documented in 14 of the 19 patients with complete angiographic follow-up.

In AVMs located in the basal ganglia, thalamus, or brainstem (n=56; median volume 3.8 cm³; median prescription dose 18 Gy) Pollock and associates found an obliteration in 43% after one radiosurgical procedure and in 57% after one or more interventions.

Volume-staged Gamma Knife Radiosurgery in Large AVM
Large AVM have a reduced chance of obliteration and increased risk for side effects after single session radiosurgery. As a result, volume-staged Gamma Knife radiosurgery has been proposed in order to reduce the risk for side effects after radiosurgery.

Volume-staged SRS for large AVMs unsuitable for surgery has potential benefit but often requires more than 2 procedures to complete the obliteration process. To have a reasonable chance of benefit, the minimum margin dose should be 17 Gy or greater.414

Patients with large AVMs underwent volume-staged Gamma Knife radiosurgery at the University of Pittsburgh School of Medicine (n=47). The median interval between the two SRS procedures was 4.9 months (range, 3-14 months). The median nidus volume was 11.5 cm$^3$ (range, 4.0-26 cm$^3$) in the first stage of SRS and 9.5 cm$^3$ in the second. The median margin dose was 16 Gy (range, 13-18 Gy) for both SRS stages. The actuarial rates of total obliteration after 2-staged SRS were 7, 20, 28 and 36% at 3, 4, 5 and 10 years, respectively. Symptomatic adverse radiation effects were detected in 13% of patients.430

In 2012 Yamamoto and colleagues described 31 patients in whom 2-stage GKS was intentionally planned at the time of initial treatment because the volume of the AVM nidus was larger than 10 cm$^3$ (mean nidus volume 16.2 cm$^3$, maximum 55.8 cm$^3$; low prescription doses: 12-16 Gy) The second GKS was scheduled for at least 36 months after the first. The cumulative complete obliteration rate in this series was 76.2% (16 of 21 eligible patients), while 22.6% experienced bleeding. The bleeding rates were 9.7%, 16.1%, 16.1%, and 26.1%, respectively, at 1, 2, 5, and 10 years post-GKS. There were 2 deaths and 3 cases of morbidity (persistent coma, mild hemimotor weakness, and hemianopsia in 1 patient each). Mild symptomatic GKS-related complications occurred in 6.5%. The rate of complications in the pediatric cases was 33.3%, whereas that in the adolescent and adult cases was 0% (p = 0.0323) 431.

The rates for complete angiographic occlusion in very large AVMs are considerably lower than in series with smaller AVMs as demonstrated in a small cohort of 18 patients with very large AVMs (> 15 cm$^3$) who underwent prospective staged-volume radiosurgery at the Langone Medical Center, New York (median AVM volume 22.9 cm$^3$; range, 15.7-50 cm$^3$). Separate anatomic volumes were
irradiated at 3- to 9-month intervals (median volume, 10.9 cm$^3$; range, 5.3-13.4 cm$^3$; median marginal dose, 15 Gy; range, 15-17 Gy). Actuarial rates of complete angiographic occlusion were 29% and 89% at 5 and 10 years, while 27.8% had a hemorrhage after radiosurgery\textsuperscript{432}.

**Retreatment after Failed Obliteration**

In general, AVMs can be retreated when the first radiosurgical session failed to provide a complete obliteration.

With regard to the additional radiation In 105 patients who had incompletely obliterated AVMs, repeat Gamma Knife radiosurgery was performed at a median of 40.9 months after initial SRS (range 27.5-139 months). Median AVM target volume was 6.4 cm$^3$ (range 0.2-26.3 cm$^3$) at initial SRS and was reduced to 2.3 cm$^3$ (range 0.1-18.2 cm$^3$) at the time of the second procedure. The median margin dose at both initial SRS and repeat SRS was 18 Gy. The actuarial rate of total obliteration by angiography or MR imaging after repeat SRS was 35%, 68%, 77%, and 80% at 3, 4, 5, and 10 years, respectively. The median time to complete angiographic or MR imaging obliteration after repeat SRS was 39 months. Factors associated with a higher rate of AVM obliteration after repeat SRS were a greater number of prior hemorrhages ($p = 0.008$), larger AVM target volume at initial SRS ($p = 0.010$). Symptomatic adverse radiation effects developed in 4.8% after initial SRS and in 9.5% after repeat SRS\textsuperscript{415}. A smaller group of patients who had undergone prospectively staged volume radiosurgery had been published earlier by the same group\textsuperscript{433}.

Repeat Gamma Knife surgery yielded a total angiographic obliteration in 55% and subtotal obliteration in 6.4% in a series of 140 patients with cerebral AVMs from the University of Virginia, Charlottesville. Although radiation-induced changes as visualized on magnetic resonance imaging occurred in 39%, only 3.6% developed permanent neurological deficits\textsuperscript{389}.

**Gamma Knife Thalamotomy for Tremor**
Medication is the standard treatment for the management of patients with movement disorders. However, in a fraction of patients with insufficient effect or bothersome side-effects of pharmaceuticals, surgical interventions are considered, among those deep brain stimulation (DBS) and surgical lesioning of the thalamus and basal ganglia as established invasive neurosurgical procedures. Lesioning in functional neurosurgery has maintained an important role in the treatment of movement disorders and a variety of lesioning technologies are still available. In a recent worldwide survey of a total of 353 neurosurgeons from 51 countries who had operated on 13,200 patients showed that ablative surgery is still used by about 65% of neurosurgeons, regardless of their country's economic status. In addition to these surgical techniques, alternatives are needed since in some patients invasive options are contraindicated. In addition, DBS is a very costly treatment with high expenses for the implanted electrodes and with necessity for changing of the implanted batteries on a regular basis.

Functional lesions can also be safely and accurately applied using radiosurgical Gamma Knife techniques. Stereotactic Gamma Knife radiosurgery provides a non-invasive alternative option in movement disorders and even in selected cases of psychosurgery. Radiosurgery can be necessary for medication-intolerable patients. The use of functional Gamma Knife lesioning to treat movement disorders is particularly attractive when surgery is contra-indicated, as sometimes in older patients and in patients with relevant co-morbidities or coagulopathies.

With a recent emphasis on health economy, the use of radiosurgery for functional lesions has regained new interest. A recent review showed that Gamma Knife thalamotomy provided favorable outcomes in the treatment of tremor, with published success rates ranging from 80-100%.

In 2013 Kooshkabadi, Kondziolka and colleagues evaluated outcomes in 86 patients who had undergone unilateral Gamma Knife thalamotomy for tremor during a 15-year period that spanned the era of MRI-based target selection (1996-2011). A single 4-mm isocenter was used to deliver a maximum dose of 140 Gy to the posterior-inferior region of the nucleus ventralis intermedius. After Gamma Knife, 66% of treated patients showed improvement in both tremor, handwriting and drinking score, 13% in 2 scores, and 2% in just 1 score. In 19% there was a failure to improve in any score. Two patients developed a temporary contralateral hemiparesis, 1 patient noted dysphagia, and 1 sustained facial sensory loss.
From June 2012 to August 2013, 7 patients with an intractable tremor underwent Gamma Knife thalamotomy with a maximal dose of 130 Gy to the left ventralis intermedius (VIM) nucleus of the thalamus at the Samsung Medical Center, Seoul, Korea. Six out of seven patients showed objective improvement in the Fahn-Tolosa-Marin tremor rating scale (TRS) score. Excluding one patient who demonstrated tremor progression, there was 28.9% improvement in the TRS score\(^4\).

In 2012 a multicenter collaborative trial at 6 Japanese institutions was conducted comprising a total of 72 patients with Parkinson disease and essential tremor who had been treated with Gamma knife thalamotomy in the lateral part of the ventralis intermedius nucleus with a single 130-Gy shot using a 4-mm collimator. **Excellent or good results were seen in 81.1% out of 53 patients who completed 24 months of follow-up**\(^\text{438}\). No permanent clinical complications were observed.

In 2010 Lim and colleagues published the outcome after unilateral Gamma Knife radiosurgery for 18 patients with disabling tremor refractory to medications who were treated at the University of Malaya, Kuala Lumpur, Malaysia. After radiosurgery the Fahn-Tolosa-Marin Tremor Rating Scale activities of daily living scores improved significantly but in this series radiosurgery provided only modest antitremor efficacy\(^\text{439}\).

In 2010 Young and associates published the outcome of VIM thalamotomy procedures with the Gamma Knife in 161 patients who underwent a total of 203 thalamotomies (119 unilateral and 42 bilateral) with a mean postoperative follow-up duration of 44 +/- 33 months. **Overall, 81% of patients showed improvements in drawing scores, for writing, 77% of patients showed improvement**\(^\text{440}\). There were side effects in 8.7%, a total of 5% were permanent. All complications were related to lesions that grew larger than expected\(^\text{440}\).

Kondziolka analyzed the outcome of 26 patients after Gamma Knife treatment for disabling essential tremor using a single 4-mm isocenter at a maximum dose of 130 or 140 Gy to the nucleus ventralis intermedius with a median follow-up of 36 months. **After radiosurgery, 69% of treated patients showed improvement in both action tremor and writing scores, 23% only in action tremor scores, and 12% in neither tremor nor writing**\(^\text{441}\). Permanent mild right hemiparesis and speech impairment developed in 1 patient 6 months after radiosurgery. Another patient had transient mild
right hemiparesis and dysphagia. 

Between 1993 and 2005 Ohye and colleagues at the Hidaka Hospital, Gunma, Japan had performed Gamma Knife radiosurgery in 70 patients with Parkinson’s disease. The thalamic reaction observed on MR or CT imaging varied with one lesion type being represented by a circumscribed round high signal area of approximately 7- to 8-mm diameter surrounding a smaller low signal area. The other is characterized by an irregular-shaped high signal zone extending into the medial thalamic area and/or the internal capsule.

Similarly in 1998 Duma published a series of 38 patients using gamma knife radiosurgery for thalamotomies to treat parkinsonian tremor (median maximum radiation dose130 Gy; range 100-165 Gy) showing excellent relief of tremor in 26% and complete abolition of tremor in 24 %. Good improvement was seen in 29%. mild improvement was seen in 10.5% and 10.5% of thalamotomies failed. The median time to onset of improvement was 2 months.

In 1999 Niranjan published a series of 15 stereotactic Gamma Knife procedures for patients with intractable tremor performed at the University of Pittsburgh Medical Center. Radiosurgery usually was performed in elderly patients with concurrent medical problems. For radiosurgery, a median dose of 140 Gy (range 130-150 Gy) was delivered using a single 4-mm collimator. Of 12 evaluable radiosurgery patients, 10 noted excellent relief and 2 had partial relief.

The average delay of clinical improvement is about 6 months after radiosurgery.

In a small series with patients suffering from multiple sclerosis tremor all 6 patients experienced improvement in tremor after a median latency period of 2.5 months after Gamma Knife. More improvement was noted in tremor amplitude than in writing and drawing ability. In four patients, the tremor reduction led to functional improvement. One patient suffered from transient contralateral hemiparesis, which resolved after brief corticosteroid administration.

Target Definition (VIM)
Sato, Ohye and associates performed depth recording around the region of the estimated optimum target and determined optimal targets as points 6-8 mm anterior to the posterior commissure, 4-6 mm dorsal to the level of the intercommissural line, and 15-17 mm lateral from the midline. Rhythmic discharge time-locked to tremor and/or kinesthetic neurons were found within the expected target area in all patients.\textsuperscript{447}

For target definition (VIM) Ohye proposed to initially refer to the posterior commissure for an approximate determination of the lateral part of the ventral intermediate nucleus. Then the point is further corrected by anatomical landmark (45% of the thalamic length) to compensate the individual difference.\textsuperscript{445} Ohye uses then Gamma Knife lesion using a 4-mm collimator, with a maximum dose of 130 Gy in 1 shot.\textsuperscript{445}

**GK thalamotomy for tremor treatment in published series. From Elaimy et al.\textsuperscript{435}**

<table>
<thead>
<tr>
<th>1st Author (Year)</th>
<th># Patients (Age Range)</th>
<th>Radiation Dose (Gy)</th>
<th>Follow-up (Range)</th>
<th>Improvement Rate</th>
<th>Complications Observed</th>
<th>Complication Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young (9) (2010)</td>
<td>161 (18-93yrs)</td>
<td>141-152</td>
<td>Mean: 44 ± 33 months</td>
<td>Drawing: 81% Writing: 77%</td>
<td>sensory loss, motor impairments, dysarthria</td>
<td>8.4%</td>
</tr>
<tr>
<td>Last Name (Year)</td>
<td>Participants</td>
<td>Age Range</td>
<td>Follow-up</td>
<td>Successful</td>
<td>Complications</td>
<td>Results</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------</td>
<td>------------</td>
<td>-----------</td>
<td>------------</td>
<td>---------------</td>
<td>---------</td>
</tr>
<tr>
<td>Lim (2010)</td>
<td>18</td>
<td>64-83 yrs</td>
<td>130-140</td>
<td>Mean: 19.2 months (7-30 months)</td>
<td>NR</td>
<td>edema, hemorrhage, dysarthria, hemiparesis, lip and finger numbness</td>
</tr>
<tr>
<td>Kondziolka (2008)</td>
<td>31</td>
<td>52-92 yrs</td>
<td>130-140</td>
<td>Median: 36 months (4-96 months)</td>
<td>92%</td>
<td>hemiparesis, dysphagia, dysarthria</td>
</tr>
<tr>
<td>Duma (1999)</td>
<td>38</td>
<td>60-84 yrs</td>
<td>120-160</td>
<td>Median: 30 months (6-72 months)</td>
<td>90%</td>
<td>dysarthria</td>
</tr>
<tr>
<td>Young (1998)</td>
<td>27</td>
<td>73.3 ± 7.2 yrs**</td>
<td>120-160</td>
<td>Mean: 22.3* months (12-44* months)</td>
<td>89%</td>
<td>none</td>
</tr>
<tr>
<td>Young (2000)</td>
<td>PD: 12</td>
<td>71.3 ± 8 yrs</td>
<td>120-160</td>
<td>&lt;12-96 months</td>
<td>PD: 88.3% ET: 92.1% Other: 50%</td>
<td>balance disturbance, paresthesias, weakness, dysphasia</td>
</tr>
<tr>
<td>Niranjan (1999)</td>
<td>12</td>
<td>38-78 yrs</td>
<td>130-150</td>
<td>Median: 24 months (4-40 months)</td>
<td>100%</td>
<td>dysarthria, weakness</td>
</tr>
<tr>
<td>Niranjan (2000)</td>
<td>11</td>
<td>38-92 yrs</td>
<td>130-150</td>
<td>Median: 6 months (2-11 months)</td>
<td>100%</td>
<td>dysarthria, weakness</td>
</tr>
</tbody>
</table>
Mathieu (2007)

Friedman (1999)

<table>
<thead>
<tr>
<th>Study</th>
<th>n (Age range)</th>
<th>Follow-up</th>
<th>Time to Symptom Improvement</th>
<th>Improvement Rate</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mathieu (2007)</td>
<td>6 (31-57 yrs)</td>
<td>130-150</td>
<td>Median: 27.5 months (5-46 months)</td>
<td>100%</td>
<td>hemiparesis</td>
</tr>
<tr>
<td>Friedman (1999)</td>
<td>15 (37-84 yrs)</td>
<td>120-140</td>
<td>3 months</td>
<td>93.3%</td>
<td>edema, incoordination, action tremor</td>
</tr>
</tbody>
</table>

Trigeminal neuralgia

Trigeminal neuralgia is a disorder of the fifth cranial (trigeminal) nerve that causes sudden bursts of intense, stabbing, electric shock-like facial pain. The prevalence is four to five per 100,000.\(^{448}\)

The recurrent pain is located in the face in the areas supplied by the trigeminal nerve. These bursts are often triggered by a light touch around the mouth or face or by talking, eating, or brushing one's teeth. Usually pain occurs unilaterally. Often medication is effective in the treatment of trigeminal neuralgia. Most frequently carbamazepine is prescribed, but carbamazepine can cause side effects
including sleepiness, forgetfulness, confusion, drowsiness, dizziness and nausea. There are other medications that can be used either alone or in combination to control trigeminal neuralgia pain. They include Lioresal (baclofen), Dilantin (phenytoin), Klonopin (clonazepam), Neurontin (gabapentin), or Lamictal (lamotrigine).

Intermittent local pressure from vascular loops on the trigeminal nerve can result in painful afferent discharge from the trigeminal nerve. For patients who continue to experience severe pain despite medication or who experience side effects from medication, an invasive surgical procedure is recommended. The most frequently applied surgical procedures are: radiofrequency electrocoagulation (RFE), glycerol injection (GLY), balloon microcompression (BMC), microvascular decompression (MVD) and Gamma Knife radiosurgery (GKRS). Some of the procedures treat the trigeminal nerve at the skull base (GLY, RFE, BMC), microvascular decompression and Gamma Knife radiosurgery treat the Trigeminal neuralgia at the origin of pain, close to the brain stem where the nerve is irritated by closely associated vessels. All of the invasive methods can be effective for periods of time, but frequently a treatment has to be repeated or combined with an alternative approach.

The neurosurgical microvascular decompression (MVD) is often effective and is generally recommended when patients are in a clinical condition that allows an invasive neurosurgical intervention. Microvascular decompression separates the trigeminal nerve from the adjacent pulsating vessel thereby removing the intermittent mechanical irritation of the nerve close to the brain stem.

Gamma Knife radiosurgery is the least invasive neurosurgical treatment for trigeminal neuralgia and achieves similar clinical results. Through highly focal irradiation of the trigeminal nerve close to the brain stem the facial pain can be treated without impairment of other neural functions. Most published series show a similar outcome with significant pain relief between 73 and 86 % of patients after the Gamma Knife intervention (see references below).

The statistics from the Leksell Gamma Knife Society demonstrate that in North America 33,194 cases with trigeminal neuralgia have been treated with Gamma Knife radiosurgery between 1991 and 2014.

Results after Gamma Knife treatment of Trigeminal Neuralgia in larger series (1968 patients)
<table>
<thead>
<tr>
<th>Study</th>
<th>year</th>
<th>target</th>
<th>number of patients</th>
<th>maximum radiation dose</th>
<th>pain free at 1 year</th>
<th>significantly improved at 1 year</th>
<th>significantly improved at 5 year</th>
<th>recurrence of pain</th>
<th>New sensory deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maesawa S, Salame C, Flickinger JC, Pirris S, Kondziolka D, Lunsford D.</td>
<td>2001</td>
<td>DREZ</td>
<td>220</td>
<td>60-90 Gy</td>
<td>70,3%</td>
<td>85,8%</td>
<td>55,8%</td>
<td>13,6%</td>
<td>10,2%</td>
</tr>
<tr>
<td>Pollock BE, Phuong LK, Foote RL, Stafford SL, Gorman DA.</td>
<td>2001</td>
<td>DREZ</td>
<td>27</td>
<td>70 Gy</td>
<td>41%</td>
<td>(at last fu)</td>
<td>24,1%</td>
<td>8%</td>
<td>(bothersome)</td>
</tr>
<tr>
<td>Pollock BE, Phuong LK, Foote RL, Stafford SL, Gorman DA.</td>
<td>2001</td>
<td>DREZ</td>
<td>61</td>
<td>90 Gy</td>
<td>61%</td>
<td>(at last fu)</td>
<td>24.1%</td>
<td>32%</td>
<td>(bothersome)</td>
</tr>
<tr>
<td>Massager N, Lorenzoni J, Devriendt D, Desmedt F, Broecht J, Levivier M.</td>
<td>2004</td>
<td>retro-gasserian</td>
<td>47</td>
<td>90Gy</td>
<td>83%</td>
<td>(good and excellent initially)</td>
<td>71%</td>
<td>(good or excellent at 42 mo)</td>
<td>8%</td>
</tr>
<tr>
<td>Sheehan J, Pan HC, Stroila M, Steiner L.</td>
<td>2005</td>
<td>DREZ</td>
<td>151</td>
<td>50-90 Gy</td>
<td>47%</td>
<td>90%</td>
<td>(some improvement)</td>
<td>70%</td>
<td>(Cave 3-y FU)</td>
</tr>
<tr>
<td>Urgosik D, Liscak R, Novotny J, Vymazal J, Vladyka V.</td>
<td>2005</td>
<td>DREZ</td>
<td>107</td>
<td>70-80Gy</td>
<td>56%</td>
<td>80%</td>
<td>25%</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Balamucki CJ, Stieber VW, CBranch et al.</td>
<td>2006</td>
<td>DREZ</td>
<td>239</td>
<td>(out of 326 treated)</td>
<td>80-90 Gy</td>
<td>56%</td>
<td>80%</td>
<td>5%</td>
<td>(very bothersome)</td>
</tr>
<tr>
<td>Longhi M, Rizzo P, Nicolato A, Foroni R, Reggio M, Gerosa M.</td>
<td>2007</td>
<td>DREZ</td>
<td>160</td>
<td>75-95 Gy</td>
<td>61%</td>
<td>90%</td>
<td>9.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Little A, Shetter AG, Shetter ME, Bay C, Rogers CL.</td>
<td>2008</td>
<td>DREZ</td>
<td>185</td>
<td>70-90 Gy</td>
<td>67%</td>
<td>(at 2 years)</td>
<td>63%</td>
<td>(7-y FU)</td>
<td>5%</td>
</tr>
<tr>
<td>Regis J, Arkha Y, Yomo S, Murata N, Roussel P, Donnet A, Peragut JC.</td>
<td>2009</td>
<td>retro-gasserian</td>
<td>334</td>
<td>80-90 Gy</td>
<td>89%</td>
<td>(initial pain relief)</td>
<td>58%</td>
<td>(painfree)</td>
<td>17%</td>
</tr>
</tbody>
</table>

**Clinical Outcome of Gamma Knife Radiosurgery for Trigeminal Neuralgia**

Kondziolka had shown in an early study of 220 patients with idiopathic Trigeminal Neuralgia who were treated with Gamma Knife radiosurgery (median maximum dose 80 Gy; range 60 -90 Gy) that...
complete pain relief was achieved in 64.9% at 6 months, in 70.3% at 1 year, and in 75.4% at 33 months while new or increased facial paresthesia or facial numbness occurred in 10%. A total of 61.4% had prior surgery. After 5 years 55.8% of patients had complete or partial pain relief. Flickinger had shown in a prospective double-blind, randomized study of patients with trigeminal neuralgia who were treated by Gamma Knife radiosurgery, that increasing the treatment volume by irradiating a longer nerve length does not significantly improve pain relief but may increase complications. Arai, Kondziolka and colleagues studied whether radiation dose rate affect clinical outcomes in patients who undergo stereotactic Gamma Knife surgery for typical trigeminal neuralgia (165 patients; maximum dose 80Gy; 4-mm collimator). The authors divided patients into a low-dose-rate group (1.21 - 2.05 Gy/minute), and a high-dose-rate group (2.06 to 3.74 Gy/minute). Initial pain relief was obtained in 71% of patients in the low-dose-rate group and 78% in the high-dose-rate group (p = 0.547). Hence the authors concluded that the GKS dose rate did not affect duration of pain control or morbidity (facial sensory dysfunction) within the range of 1.21-3.74 Gy/minute. The use of carbamazepine or gabapentin at the time of radiosurgery does not decrease the rates of obtaining partial or complete pain relief after radiosurgery, but gabapentin may reduce the risks of developing post-radiosurgery trigeminal neuropathy.

Between July 1992 and November 2010, 497 patients presenting with trigeminal neuralgia underwent a single Gamma Knife treatment and prospective evaluation with a follow-up longer than 1 year at Timone University Hospital in Marseille, France. Megadolichobasilar artery- or multiple sclerosis-related trigeminal neuralgia were excluded. A single 4-mm isocenter was positioned in the cisternal portion of the trigeminal nerve at a median distance of 7.8 mm (range 4.5-14 mm) anterior to the emergence of the nerve. A median maximum dose of 85 Gy (range 70-90 Gy) was delivered. Median follow-up period was 43.75 months (range 12-174.41 months). A total of 91.34% were initially pain free within a median time of 10 days (range 1-459 days) after GKS. A substantial number of patients (37.2%) became pain free within the first 48 hours and 42.8% between posttreatment Day 3 and Day 30, and 20% after 30 days post-GKS. Out of the patients who initially became free from pain, 34.4% experienced a recurrence of pain with a median delay of 24 months (range 0.62-150.06 months).

In 2014 the actuarial rate of freedom from pain recurrence (BNI scores I-III) of 149 cases with
therapy refractory trigeminal neuralgia treated with Gamma Knife stereotactic radiosurgery at the William Beaumont Hospital, Royal Oak were 76%, 69% and 60%, at 1, 2 and 3-years respectively. Toxicity after first GK SRS was minimal with 25% of cases experiencing only new or worsening post-treatment numbness 454.

Between 1999 and 2008, 446 of 777 patients with trigeminal neuralgia underwent Gamma Knife radiosurgery at the Wake Forest Baptist Medical Center, Winston-Salem, North Carolina and had evaluable follow-up (median follow-up 21.2 months). Rates of freedom from BNI 4-5 failure at 1, 3, and 5 years were 84.5%, 70.4%, and 46.9%, respectively. While 42% of patients developed trigeminal dysfunction, multivariate analysis revealed that post-SRS numbness and improved post-SRS BNI score at 6 months were predictive of a durable pain response 455.

In 2013 Young and colleagues followed up on 250 consecutive patients treated with the Leksell Gamma Knife unit using a 4-mm isocenter. The isocenter had been placed on the trigeminal nerve with the 20% isodose line tangential to the pontine surface (18 Gy). A total of 71.4% were pain free (Classes I and II) and 89.5% had at least 50% pain relief: 43.7% were pain free without medication; 27.7% were pain free with medication, there was more than 90% decrease in pain intensity in 9.7%, and decrease in pain intensity 8.4%, and 50%-90% decrease in pain intensity in 8.4%, less than 50% decrease in pain intensity in 4.6%, and pain became worse in 5.9%. Increase in numbness intensity after GKS was associated with a decrease in pain intensity and pain length (p < 0.05) 456.

In 2013 Elaimy, Lee and colleagues presented the outcome of 108 patients treated at Gamma Knife of Spokane for typical trigeminal neuralgia in a median clinical follow-up time of 15 months. Following the first GKRS procedure, 71% of patients were grouped into BNI class I-IIib (I = 31%; II = 3%; IIIa = 19%; IIIb = 18%) and the median duration of pain relief for those patients was determined to be 11.8 months. New facial numbness was reported in 19% of patients and new facial paresthesias were reported in 7% of patients after the first GKRS procedure. Following a second GKRS procedure (n=19), 73% of patients were grouped into BNI class I-IIib (I = 44%; II = 6%; IIIa = 17%, IIIb = 6%) and the median duration of pain relief for those patients was determined to be 4.9 months. For repeat procedures, new facial numbness was reported in 22% of patients and new facial paresthesias were reported in 6% of patients 457.
In the post radiosurgical follow-up, tractography was more sensitive than conventional gadolinium-enhanced post-treatment MR to detect changes in the trigeminal nerve. Diffusion tensor imaging (DTI) provides information on white matter microstructure. DTI parameters accurately detect the effects of focal radiosurgery on the trigeminal nerve, serving as an in vivo imaging tool to study trigeminal neuralgia. Radial diffusivities but not axial diffusivities changed markedly, suggesting that radiosurgery primarily affects myelin. 458.

In 2012 Li reported on 129 patients with idiopathic trigeminal neuralgia who had undergone Gamma-knife radiosurgery at the West China Hospital of Sichuan University (maximum dose 80-90 Gy; mean follow-up 29.6 months) that 84.5% had complete or partial pain relief and a recurrence after a mean time of 12.7 months in 8.3% of the initially successfully treated patients. A mild-to-moderate facial numbness occurred in 38% 459.

In the same year Loescher, Rowe and associates reported the outcome of 72 patients treated with Gamma-knife radiosurgery (maximal dose 80 Gy) at the National Centre for Stereotactic Radiosurgery in Sheffield, UK. The percentage of patients who were pain free without medication was 39% after 6 months, 36% after 12 months and 64% after 24 months. The percentage of patients who reported being very satisfied with treatment was 71% after 6 months, 57% after 12 months and 53% after 24 months. A new trigeminal sensory deficit was reported by 31% of patients after radiosurgical treatment 460.

Hayashi, Takakura and colleagues from Tokyo Women's Medical University applied a maximum dose of 90Gy in 130 patients with trigeminal neuralgia, who were treated using Leksell Gamma Knife and reported a marked initial relief of the typical paroxysmal facial pain in 98% (n=127) within a median interval of 3 weeks after treatment. Since the pain re-appeared later in 23 patients, at the time of the last follow-up 86% 86% were pain-free (n=112). In 24% facial hypesthesia and/or paresthesia occurred 461.

In 2010 Verheul, Beute and colleagues had reviewed 365 patents with medically refractory trigeminal neuralgia, who were treated at the Gamma Knife Center Tilburg, Netherlands. In all patients 80 Gy was prescribed, with a single 4-mm isocenter located at the root entry zone. In the idiopathic trigeminal neuralgia group, rates of adequate pain relief were 75%, 60%, and 58% at 1, 3, and 5 years, respectively. Somewhat bothersome numbness was reported by 6% of patients after
the first treatment and by 24% after repeated GKS. Very bothersome numbness was reported in 0.5% after the first GKS and in 2% after the second treatment.462

In the same year Kano, Lunsford and colleagues had retrospectively reviewed outcomes after Gamma Knife radiosurgery for recurrent trigeminal neuralgia after failed surgery in 193 patients. After Gamma Knife, 85% of patients achieved pain relief or improvement. Pain recurrence was observed in 73 of 168 patients 6 to 144 months after GKSR (median, 6 years). Factors associated with better long-term pain relief included no relief from the surgical procedure preceding GKSR, pain in a single branch, typical TN, and a single previous failed surgical procedure. Eighteen patients (9.3%) developed new or increased trigeminal sensory dysfunction, and 1 developed deafferentation pain. Patients who developed sensory loss after GKSR had better long-term pain control. The best candidates for Gamma Knife were patients with recurrence after a single failed previous operation and those with typical TN in a single trigeminal nerve distribution.463

A series of 53 patients with trigeminal neuralgia who underwent a single Gamma Knife treatment were followed by a minimum follow-up of 36 months at Tufts Medical Center (maximum dose 80 Gy, a single 4-mm isocenter). Complete pain relief without medications was seen in 32.1% of patients, complete pain relief with either a decrease or no change in medications in 1.9%; ≥ 50% pain relief without medications in 3.8%; ≥ 50% pain relief with either a decrease or no change in medications in 20.8% and < 50% pain relief and/or increase in medications in 41.5%.464

In 2009 Regis, Peragut and colleagues reviewed the outcome of 262 patients with minimum of 1 year of follow-up after Gamma Knife treatment for trigeminal neuralgia targeting the retrogasserian cisternal portion of the Vth cranial nerve (median maximal dose 85Gy; range: 70-90). At 5 years, 58% of the patients remain pain-free and 83% had no trigeminal nerve disturbance. The median delay for pain cessation was 15 days. The initial pain-relief rate was 89%.465

In a study from Université de Sherbrooke, Quebec, Canada, Knafo, Mathieu et al. showed significant pain relief in 77.6% of patients after Gamma knife (n=67), including 32.6% who became pain-free with sensory side effects in 14.9%.466
Little, Rogers and colleagues studied the long-term outcome of patients treated with gamma knife radiosurgery for typical trigeminal neuralgia in 136 patients at the Barrow Neurological Institute in Phoenix, Arizona with clinical follow-up data of more than 4 years (maximum dose 80 Gy targeted at the root entry zone). Actuarial analysis demonstrated that 32% of patients were pain-free off medication and 63% had at least a good outcome at 7 years. When GKRS was used as the primary treatment, 45% of the patients were pain-free at 7 years. Treatment failed in 33% of the cohort within 2 years, but only an additional 1% relapsed after 4 years. Posttreatment facial numbness was reported as very bothersome in 5% 467.

In 160 patients with trigeminal neuralgia refractory to medical therapy Longhi, Gerosa and colleagues reported a Grade I outcome in 61% and a Grade II outcome in 29%. In 10% Gamma Knife had no effect 468.

In 2005 Sheehan, Steiner and associates had reported 151 cases of trigeminal neuralgia who had been treated with Gamma knife (maximal radiation doses ranged from 50 to 90 Gy; median follow up 19 months; range 2-96 months). The mean time to relief of pain was 24 days (range 1-180 days). At the 1-, 2-, and 3-year follow-up, 47%, 45%, and 34% of patients, respectively, were pain free without medication and 90%, 77%, and 70% of patients experienced some improvement in pain at the 1-, 2-, and 3-year follow ups, respectively, while 27% of patients with initial improvement subsequently experienced pain recurrence a median of 12 months (range 2-34 months) post-Gamma Knife. New facial numbness was seen in 9% post-GKS. At the last follow up, GKS effected pain relief in 44% of patients. Some degree of pain improvement at 3 years post-GKS was noted in 70% of patients with TN 469.

**Trigeminal Neuralgia Related to Multiple Sclerosis**

Among patients with multiple sclerosis there is a high incidence of trigeminal neuralgia, and outcomes after treatment seem inferior to those in patients suffering from idiopathic trigeminal neuralgia.

Patients with Trigeminal neuralgia related to multiple sclerosis with more than 1 year of follow-up were operated with Gamma Knife radiosurgery and prospectively evaluated in the Timone
University Hospital, Marseille (n=43). A single 4-mm isocenter was positioned at a median distance of 8 mm anterior to the emergence of the nerve. A median maximum dose of 85 Gy (range 75-90) was delivered. The median follow-up period was 53.8 months (12-157.1). While 90.7% were initially pain free, the actuarial probability of remaining pain free without medication at 6 months, 1, 3 and 5 years was 87.2, 71.8, 43.1 and 38.3%, respectively. The hypoesthesia actuarial rate at 6 months, 1 and 2 years was 11.5, 11.5 and 16%, and remained stable till 12 years. In the multiple sclerosis-related trigeminal neuralgia group from Tilburg, Netherlands, the rates of adequate pain relief were reported to be 56%, 30%, and 20% at 1, 3, and 5 years after Gamma Knife treatment, respectively.

In 2012 Mathieu, Séguin and colleagues retrospectively compared the clinical outcomes in patients with MS-related trigeminal neuralgia after Gamma Knife surgery with those obtained using percutaneous retrogasserian glycerol rhizotomy in 45 patients with multiple sclerosis-related TN. Reasonable pain control (BNI Pain Scale Scores I-IIib) was noted in 81.5% who underwent GKS and in 100% who underwent PRGR. For patients who underwent GKS, the median time to pain relief was 6 months; for those who underwent PRGR, pain relief was immediate. As of the last follow-up after a median of 39 months, complete or reasonable pain control was finally achieved in 85.2% in the GKS group and in 88.9% in the percutaneous retrogasserian glycerol rhizotomy group. The morbidity rate was 22.2% in the GKS group (all due to sensory loss and paresthesia) and 66.7% in the percutaneous retrogasserian glycerol rhizotomy group (mostly hypalgesia, with 2 patients having corneal reflex loss and 1 patient suffering from meningitis). It can be concluded from this study that Gamma Knife surgery has a lower rate of sensory and overall morbidity than percutaneous retrogasserian glycerol rhizotomy.

Treatment Doses (Trigeminal Neuralgia)

In Gamma Knife radiosurgery of trigeminal neuralgia typically maximum doses of 80-85 Gy are applied in a single isocenter using a 4-mm collimator.

Initially Kondziolka had shown in 1996 that a maximum radiosurgical dose of > 70 Gy was associated with a significantly greater chance of complete pain relief (72% vs. 9%, p = 0.0003). Pollock had compared a group of patients treated at maximum doses of 90Gy vs 70Gy. At last follow-up
examination, 41% of the low-dose group remained pain-free compared with 61% high-dose cohort (P = 0.17). High-dose radiosurgery was associated with an increased rate of permanent trigeminal nerve dysfunction (54% versus 15%, P = 0.003) and among high-dose patients 8% developed corneal numbness and 32% bothersome dysesthesias, whereas only 1 low-dose patient had this complication (P = 0.01). The authors concluded that the incidence of significant trigeminal nerve dysfunction is markedly increased after radiosurgery for patients receiving maximum doses of 90Gy.

Flickinger had shown in a prospective double-blind, randomized study that increasing the treatment volume to include a longer nerve length for trigeminal neuralgia radiosurgery does not significantly improve pain relief but may increase complications. The Gamma Knife dose rate does not affect duration of pain control or morbidity. Similarly Balamucki, Branch and colleagues had previously examined whether the decrease in dose rate over 4.6 years between Co source replacements affected the control rates of facial pain in patients undergoing Gamma Knife treatment (239 procedures) showing that dose rate was not significantly associated with either the control rate or degree of pain relief.

**Target Location (Trigeminal Neuralgia)**

The typical target point the in Gamma Knife radiosurgery of trigeminal neuralgia is the trigeminal nerve either at its dorsal root entry zone or slightly further anterior in the nerve’s retrogasserian portion. While initially the target point in the dorsal root entry zone had been introduced, Regis proposed to use an anterior ‘retrogasserian’ target in order to avoid the rather constant occurrence of paraesthesia or facial numbness that was associated with the more posterior target point.

Regis demonstrated in 83 patients who had been treated with gamma knife surgery to the retrogasserian cisternal portion of the fifth cranial nerve at a typical maximum dose of 85 Gy (range 70-90 Gy) that 70% (58/83) had stopped taking medication during the study and that all quality-of-life parameters were improved (p < 0.001). With this modified target point only 7.2% (6/83) reported facial generally mild paresthesia, and 4.8% reported mild hypesthesia.

In 2008 Matsuda, Ono and colleagues compared results using the two Gamma Knife target points, the dorsal root entry zone and the retrogasserian portion, in a series of 100 patients with intractable
trigeminal neuralgia by applying 80 Gy at the proximal trigeminal nerve (posterior group) or 90 Gy at the retrogasserian portion (anterior group). The rate of initial complete remission was higher in the posterior group than in the anterior group (p = 0.003). Against expectations, more complications were observed in the anterior group than in the posterior group (p = 0.009). The authors found that the posterior targeting group had better pain control and a lower complication rate.476

A subgroup of 65 patients was studied for whom 6-month follow-up MRI showed focal contrast enhancement of the trigeminal nerve showing that the median deviation of the coordinates between the intended target and the center of contrast enhancement was 0.91 mm in Euclidean space. The radiation doses fitting within the borders of the contrast enhancement of the trigeminal nerve root ranged from 49 to 85 Gy (median value, 77 +/- 8.7 Gy). The median deviation found in clinical assessment of gamma knife treatment for trigeminal neuralgia is low and compatible with its high rate of efficiency.477

Retreatment with Gamma Knife (Trigeminal Neuralgia)

In patients with recurrent pain after radiosurgery, the treatment can be repeated. Repeat Gamma Knife radiosurgery was performed in 119 patients with recurrent trigeminal neuralgia. The median interval between procedures was 26 months. The median target dose for repeat Gamma Knife was 70 Gy (range, 50-90 Gy) and the median cumulative dose was 145 Gy (range, 120-170 Gy). The median follow-up was 48 months (range, 6-187 months) after repeat GKSR. After repeat Gamma Knife, 87% of patients achieved initial pain relief (Barrow Neurological Institute pain score I-IIIb). Pain relief was maintained at 1 year in 87.8%, at 3 years in 69.8% and at 5 years in 44.2%, respectively. Facial sensory dysfunction occurred in 21% of patients within 18 months after GKSR. A cumulative edge of brainstem dose ≥ 44 Gy was more likely to be associated with the development of sensory loss. The best responses were observed in patients who had good pain control after the first procedure and those who developed new sensory dysfunction in the affected trigeminal distribution.478 The rate of pain relief of 27 patients who underwent repeat GK SRS at the William Beaumont Hospital, Royal Oak was 70% and 62% at 1 and 2 years, respectively.454

In patients unsuitable for other microsurgical or percutaneous strategies, especially those receiving
long-term oral anticoagulation or antiplatelet agents, Gamma Knife radiosurgery repeated for a third time may be a satisfactory, low risk option.

In 2015 a retrospective review of all patients who underwent 3 Gamma Knife radiosurgery procedures for trigeminal neuralgia at 4 participating centers of the North American Gamma Knife Consortium from 1995 to 2012 was performed and 17 patients were identified; **47.1% reported initial complete pain relief following their third Gamma Knife radiosurgery and 47.1% experienced at least partial relief.** The average time to initial response was 2.9 months following the third Gamma Knife radiosurgery. **Although 17.6% developed new facial sensory dysfunction following primary Gamma Knife radiosurgery and 2 patients 11.8% experienced new or worsening sensory disturbance following the second Gamma Knife radiosurgery, no patient sustained additional sensory disturbances after the third procedure.** At a mean interval of 19.1 months following the third Gamma Knife treatment, 23.5% suffered from recurrent trigeminal neuralgia.

**Comparative effectiveness: Gamma Knife vs. Microvascular Decompression**

It is virtually impossible to compare a highly invasive treatment such as microvascular decompression with a non-invasive option such as Gamma Knife radiosurgery, since in general, the non-invasive option is chosen in order to avoid the associated side-effects and complications associated with the open neurosurgical procedure. Frequently Gamma Knife is applied in elderly patients or in patients with relevant co-morbidities, when a highly invasive microvascular decompression cannot be carried out at a low risk level.

In elderly patients Oh, Lim and associates compared the outcome after micro-vascular decompression (MVD) with Gamma knife radiosurgery (GKRS). According to Pain Intensity Scale, MVD group showed better prognosis with 63% (n=17) cases in grade I-II versus 55.6% (n=10) in GKRS group after the treatment. The rate for recurrence of pain (11.1 %) was identical for both treatment options. **After the treatment, 2 cases of facial numbness, and 1 case each of herpes zoster, cerebrospinal fluid (CSF) leakage, hearing disturbance, and subdural hematoma occurred in MVD Group. In GKRS, there was 1 (5.6%) case of dysesthesia but was not permanent.**
Linskey compared his experience with microvascular decompression ([MVD], 36 patients) and Gamma Knife surgery ([GKS], 44 patients) in 80 consecutive patients with trigeminal neuralgia. Respective initial and latest follow-up raw pain-free rates were 100 and 80.6% for MVD and 77.3 and 45.5% for GKS. The median time to the maximal benefit after GKS was 4 weeks (range 1 week-6 months). Respective initial, 2-, and 5-year actuarial pain-free rates were 100, 88, and 80% for MVD and 78, 50, and 33% for GKS ($p = 0.0002$). The rates of permanent mild and severe sensory loss were 5.6 and 0% for patients in the MVD group, as opposed to 6.8 and 2.3% for patients in the GKS group. Anesthesia dolorosa did not occur during the study. Both procedures enjoyed a high degree of early patient satisfaction (95-100%). Microvascular decompression maintained the same rate of patient satisfaction, but satisfaction with GKS decreased to 75% as pain control waned. In the MVD group there were complications of cerebrospinal fluid leakage, hearing loss, and persistent diplopia (1 case each in the MVD group), which were not seen after Gamma Knife 481.

In cases of failed Gamma Knife radiosurgery for trigeminal neuralgia a trigeminal micro-vascular decompression still remains a viable alternative if further surgery is required, as in surgery after Gamma Knife no apparent changes in the trigeminal nerve itself or in any other tissue were found that would have made surgery technically more difficult. 482.

It can be concluded that, despite the delayed and slightly lower degree of pain relief, for trigeminal neuralgia patients with advanced age or in patients with co-morbidities precluding an open invasive neurosurgical procedure, Gamma Knife radiosurgery can be preferable due to the lower rate of surgical complications that arise owing to the old age 480.


27. Langley RE, Stephens RJ, Nankivell M, et al. Interim data from the Medical Research Council QUARTZ Trial: does whole brain radiotherapy affect the survival and quality of life of


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