State of the Art of **Gamma Knife Radiosurgery**

2014

An Overview of Current Practice and Review of the 17th International Leksell Gamma Knife Society Meeting
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Selected videos and PDFs of most of the presentations given at the 17th International Leksell Gamma Knife Society may be accessed at www.lgksociety.com. For more information on the subject matter contained herein, please contact info@lgksociety.com.
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Clinical Overview

Bodo Lippitz, MD

Introduction

This section is a summary and analysis of the clinical proceedings of the 17th International Meeting of the Leksell Gamma Knife Society held in New York in May, 2014. A total of 300 abstracts were presented reflecting the current stage of development and research in Gamma Knife radiosurgery.

Although it would have been an option to analyze the proceedings of the current meeting only according to the most novel trends or according to the largest studies or randomized trials, the variety of indications for Gamma Knife radiosurgery (GKRS) demands a broader view. The focus of this review is a general overview plus recording and preservation of scientifically and practically valuable data that were presented at the meeting. Hence, for practical reasons, doses, volumes and the length of follow-up are generally included when provided in a cited presentation. When greater discrepancies between abstract and slides were noted, the data from the slides were cited, since it was assumed that they represent the more recent analyses. Due to space and format, not all presentations appear in this summary. In such a review it is virtually impossible to summarize presentations that provide a general overview of a specific field. The result is that several of highly relevant comprehensive reviews cannot be included here, since the complexity of the topic would not allow a short summary in the given space. Very few and generally those that represent a novel approach, were selected; in some cases these presentations were not even associated with radiosurgery.

Indications treated worldwide 1991 - 2013

- Malignant Tumors: 354,605
- Benign Tumors: 295,840
- Vascular disorders: 96,862
- Functional disorders: 54,957
- Other disorders: 3,057

- Malignant Tumors: 44%
- Benign Tumors: 37%
- Vascular disorders: 12%
- Functional disorders: 7%
- Other disorders: 0%

68-100% sites reporting 1991 reflects cumulative numbers
The Leksell Gamma Knife Society Meeting provided many practical hints for daily clinical practice, but apart from the detailed review, it is tempting to see if there are more general tendencies that can be sensed through the abundance of data. Several comprehensive trends increasingly appear to materialize:

1. **Larger study groups are being established** to organize retrospective and prospective trials that will change daily clinical practice through large numbers and higher quality evidence. Examples are the European Gamma Knife Society (EGKS) meningioma analysis, the North American Gamma Knife Consortium (NAGKC) studies and the studies conducted by the Japanese Leksell Gamma Knife Society (JLGK) Study Group.

2. **Gamma Knife radiosurgery has become an inherent component in the treatment of neurological conditions and clinical practice and scientific studies increasingly integrate radiosurgery in a combined approach.** This is true in surgery, where Leksell Gamma Knife® provides the ability to reduce the morbidity of the intervention or in chemotherapy, where Gamma Knife treats brain metastases that are inaccessible for medication. Hence, even cancer patients with brain metastases can benefit from recent progresses in targeted systemic therapy with improved life expectancy.

3. **The fact that the number of brain metastases is not directly related to the patient’s prognosis is now being realized.** The logical conclusion is the necessity to treat all of these metastases effectively in order to maintain the patient’s quality of life. Important studies have now provided the necessary data. It has now been realized that the previously assumed limitation of radiosurgical indications that was based on a defined number of brain metastases, was a mere artifact of previous study designs. This conclusion will lead to an exponential increase of patients with brain metastases being treated with stereotactic radiosurgery.

4. **The trend toward fractionated stereotactic radiosurgery that was visible at the two recent ISRS meetings has not quite reached the Gamma Knife community, although an increasing number of studies document fractionation schemes in larger benign and malignant tumors.**

5. **The radiosurgical salvage treatment of anaplastic gliomas and glioblastomas has recently been cleared by the FDA and a number of studies show reproducible results that demonstrate that Gamma Knife radiosurgery can be an additional treatment option in this otherwise highly problematic condition.**

6. **Lesioning in functional neurosurgery has maintained its role, since deep brain stimulation is associated with high costs, maintenance problems and specific side effects.** A majority of functional neurosurgeons is still applying lesioning techniques and the number of functional lesioning procedures appears to be increasing again. Leksell Gamma Knife® has become an important non-invasive alternative in lesioning and results document a clinical efficacy identical to invasive methods.
Brain Metastases

According to conservative estimates, about 8% of cancer patients will develop brain metastases, which often cause the leading symptoms in cancer. Chemotherapy has significantly improved the prognosis of patients with cancer but generally fails in the treatment of brain metastases. Hence, many chemotherapeutical regimens are not applicable in the presence of brain metastases.

An effective therapy and local tumor control is paramount for the patient’s prognosis and quality of life. In practice, conventional fractionated whole brain radiotherapy (WBRT) is still frequently applied as a standard therapy of brain metastases, but side effects and lack of sustained local efficacy could outweigh potential benefits: The median survival of patients with brain metastases treated with WBRT appears to be very limited and was less than 4.5 months in 8 out of 9 studies in 1925 out of 1971 reported patients. In patients with adverse prognostic features there was no significant difference between best supportive care and 20 Gy WBRT and only slight and clinically irrelevant differences in the 30 Gy WBRT group (median 2.2 vs. 1.7 months).

These results match the recently published interim data from the QUARTZ Trial (Quality of Life after Radiotherapy for Brain Metastases), a randomized Phase III trial of patients with inoperable NSCLC brain metastases showing a median survival of 49 days after optimal supportive care plus WBRT. On the other hand, WBRT must be considered insufficient in patients with a better systemic prognosis, since prospective and randomized studies showed that WBRT provided only limited local control over the treated brain metastases with complete or partial responses in 24-55%. WBRT in brain metastases of colorectal cancer (3 Gy x 10) achieved a local control of 17% at six months.
The application of focal radiation using Gamma Knife radiosurgery (GKRS) has changed these previously rather negative perspectives in a fundamental way. Reproducible tumor control after radiosurgery underlines that physically focused and stereotactically applied radiation can overcome several limitations of fractionated radiotherapy. This insight has significantly influenced treatment recommendations and guidelines that have recently been published to define the criteria for treatment of brain metastases from a surgical, radiotherapeutical and radiosurgical perspective. In practical terms radiosurgery is still an unusual treatment, as only 6.1% of 7684 patients with non-small cell lung cancer who were diagnosed with brain metastases in the US between 2000 and 2007 had billing codes for stereotactic radiosurgery, while radiosurgery was significantly associated with increasing year of diagnosis, higher socioeconomic status and admission to a teaching hospital.

According to an international online practice survey in 2010 with 445 responses, 93% from radiation oncologists, 78% of respondents would still use WBRT alone for initial treatment of two to four brain metastases in patients with a KPS of 70 and active, uncontrolled extracranial disease.

The trends for Gamma Knife radiosurgery indications over time are well reflected by a review of indications and clinical practice at the Cleveland Clinic, where a significant change in indications was seen between 2002-12. Until 2012, the number of patients who underwent Gamma Knife treatment increased from 148 to 349 and the increase in total patients (201 more in 2012 than 2002) is almost completely accounted for by the parallel increase in patients treated for metastasis. The metastasis subgroup showed a concurrent increase in mean number of metastases treated per patient. Despite a decrease in per patient billing of 36%, case volume and indications suggest an estimated total billing increase of 150% between 2002 and 2012.
Improved Detection of Metastases: Time-Delayed MRI and NeMO

Due to the improved image quality in immobilized patients in stereotactic frames and due to the use of increased doses of Gadolinium, frame-based stereotactic MRI studies detect generally 34-40% more metastases than anticipated from diagnostic studies. A supporting study was presented showing that 6% of patients had an increased number of lesions on the day of GK than on pre-operative imaging when the slice thickness decreased from 3-5 mm to 1-2 mm.

The T2-weighted images from the 7T brain MRI reveal detailed microvasculature and the internal contents of supratentorial brain tumors better than that of the 1.5T brain MRI. However, for brain tumors located in parasellar areas or areas adjacent to major cerebral vessels, flow-related artifacts are exaggerated in the 7.0T brain MRIs. For brain tumors adjacent to skull base, susceptibility artifacts in the interfacing areas of paranasal sinus and skull base hampered the acquisition of detailed images and information on brain tumors in the 7.0T brain MRIs.

Contrast enhancement of metastases is a dynamic process. For example, delaying imaging for 10-25 minutes after contrast administration reveals additional brain metastases in a substantial number of patients and permits radiosurgical treatment for all detectable tumors. Between the 1st and 3rd scan 15 minutes after contrast administration, 41.2% of subjects had new brain metastases identified, with an increase range of 1-14.

When the goal is to improve tumor detection in the follow-up, identifying additional brain metastases or areas of subtle tumor growth in benign brain tumors, a simple method can be helpful: subtracting prior (old) high-resolution MR images from new stereotactic MR images creates New-Minus-Old (NeMO) fusion images, thus highlighting areas of change that developed in the time interval between the two scans. After reviewing 100 new-old subtraction-fusion images, 33 additional brain metastases most commonly near dura and blood vessels were identified from 24/100 radiosurgery sessions.

Feasibility of Gamma Knife Treatment of Multiple Brain Metastases and Comparison with Alternative Technologies

Several studies compared the radiation dose exposure to normal brain in Gamma Knife compared with various alternative radiation techniques and demonstrated that Leksell Gamma Knife® was superior in reducing the dose to normal structures. Different quality metrics were used to compare radiosurgery plans for multiple metastases generated for treatment with Leksell Gamma Knife Perfexion (GKP) and single-isocenter volumetric modulated arc radiosurgery (VMAS). Plans that showed similar dose conformality and PTV coverage, also showed significantly increased low-dose spillage for single-isocenter volumetric modulated arc radiosurgery plans. The peripheral normal brain tissue doses were lowest for the Gamma Knife Perfexion and highest for TrueBeam FFF and CyberKnife treatment plans. Comparing the volumes of normal brain receiving 12 Gy, True-Beam FFF, Novalis and Cyber-Knife were 180-290% higher than Gamma Knife Perfexion. Each successive hardware/software version generally showed an improvement to the treatment plan in terms of coverage, selectivity and PCI.
Plans produced with Leksell GammaPlan® 10.1 were better with regard to all planning parameters. A typical SRS case is unlikely to reach the whole brain limit of 800cGy even when 35 mixed lesions or 68cc were treated. During treatment of multiple brain metastases the Gamma Knife Perfexion gave low doses to the brain (mean 1.03 Gy, median 0.90 Gy). No correlation was found between the mean dose to the head and the total number of metastases treated. The conclusion was that radiosurgery for multiple lesions, when performed with the Gamma Knife, exposes the normal brain to relatively low doses, which allows even multiple treatments if necessary.

Dose-Volume Histograms for Linac WBRT 30 Gy, Tomotherapy 30 Gy with 10 Gy boost and Gamma Knife treatment of 28 brain metastases (18 Gy min dose, 11.4 cc total volume) From Ian Paddick

Metastases and Quality of Life

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. 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. Subacute 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 12 months after fractionated radiotherapy is a known phenomenon. It was 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.

It can be considered as proven that GKRS allows the maintenance of the quality of life in patients with brain metastases. Supporting evidence was presented in 317 patients who underwent Gamma Knife treatment for brain metastases and completed initial quality of life (QOL) questionnaires at 3, 6, and 12 months posttreatment. QOL is largely preserved following GKRS (with or without surgery), with statistically significant improvements measured throughout the first year of follow-up. In contrast, patients undergoing whole brain radiotherapy in addition to GKRS experienced initial improvement and subsequent decline in QOL through the first post-treatment year. Another study confirmed these results in 97 consecutive patients with 1-6 brain metastases and showed that quality of life remained stable for at least 12 months following GKRS. The highest QOL is seen for patients with improved or stable cerebral symptoms, reflecting local tumor control.
Metastases: Age

Three published randomized controlled trials ((EORTC 22952-26001, JRSOG99-1 and MDACC NCT00548756) comparing patients assigned to SRS alone vs. SRS plus WBRT for newly diagnosed 1 to 4 brain metastases were individually under-powered for overall survival (OS) comparisons. The raw individual patient data from 364 patients receiving either SRS alone or SRS plus WBRT were reevaluated in a meta-analysis. The result showed a statistically significant favorable treatment effect on overall survival for patients age ≤50 years who had been treated with stereotactic radiosurgery alone. In this age group, distant brain relapse rates were not increased, despite omission of upfront WBRT. According to this re-evaluation of prospective randomized data, WBRT offered no advantage in this age group18.

On the other hand, treatment results after SRS for brain metastases in patients over age 80 (n=165) were compared with the outcome of patients who were 65-79 years old (n=1181). Although post-SRS median survival time in patients over age 80 (5.3) was shorter than patients 65-79 years old (6.9), this difference was not statistically significant. Competing risk analyses showed that the two groups did not differ significantly in cumulative incidences of local recurrence, repeat SRS, neurological deterioration or SRS related complications. Hence, older patients do not appear to be poor candidates for SRS19.

Large metastases

There is a general agreement that larger brain metastases with a clinically relevant mass effect should be removed surgically as single session radiosurgery in larger brain metastases can be associated with side effects due to later formation of edema. These difficulties in the radiosurgical treatment of large volumes were documented in series of 143 patients with single large brain metastases (>10 cc), where in 37% local tumor progression and/or increase in perilesional edema was seen after radiosurgery20. The alternatives for larger brain metastases are the surgical resection or the recently applied hypofractionated stereotactic radiosurgical therapy. A three-staged gamma knife treatment for large brain metastases (>10cc in volume) has been proposed using a prescription dose of 10 Gy in three fractions21. A study was presented where the efficacy of 3-staged radiosurgery compared with 2-staged stereotactic radiation therapy in 211 large brain metastases: 124 metastases in 119 patients were treated with 2-staged SRT (Group A) and 87 lesions in 83 patients were treated with 3-staged SRT (Group B). The prescribed dose was 26 to 28 Gy in 2 fractions with 2-4 weeks interfraction in Group A, (n= 124); and 30 Gy in 3 fractions with 2 weeks interfraction in Group B (n=87). The mean tumor volume was 18.6 cc (range 10.0 to 51.1). The median overall survival period was 7.4 and 9.7 months in groups A and B, respectively. The results revealed that the treatment result of 2-staged SRT would be equivalent to 3-staged SRT22. Unfortunately the study did not provide data concerning morbidity or ARE22.
Cystic Metastases

Cystic brain metastases (n=37) showed actuarial local tumor control rates of 92.9% and 82.2% at 6 and 12 months, respectively. Adequate doses should be applied, since local 12-month tumor control rates of lesions treated with margin doses <15 Gy were 64% whereas 91% of metastases that had been treated with prescription doses >15 Gy were controlled. Cystic metastases of colorectal origin demonstrated the best treatment response of the cystic component, significantly higher than metastases from the breast, but not the lung.

Brainstem Metastases

Brainstem metastases (n=28) that were treated with a median dose of 17 Gy showed a crude local control rate of 88%, but an actuarial overall survival at one year of only 13% with a median overall survival of 4.6 months. Very similar results were shown in another study: at an average GKRS prescription dose of 17 Gy, local tumor control was achieved in 91% and the post-GKRS overall survival at 6-months was 42%, at 12-months 22%. There were no serious complications of GKRS.

Calvarial Metastases

Calvarial metastases are unusual targets in radiosurgery and are often declined since there is uncertainty concerning threshold doses for the skin. In seven patients with calvarial lesions treated with GKRS, a novel technique was utilized with bolus placement over the site of treatment (median prescription dose 15 Gy). The 1-year local control rate was 88.9%. None of the patients treated to calvarial sites in this study had worsening of their local symptoms after radiosurgical treatment or suffered a complication due to this particular treatment technique (data from slide).

Gamma Knife radiosurgery plans for a patient with a history of breast cancer with three concurrent metastases to the calvarial bones with extension through the inner table into the underlying dura. The superficial border of the bolus skin-equivalent layer is outlined in red. From Rupesh Kotecha.
Adjuvant Gamma Knife Radiosurgery for Resected Metastases

Due to high risk of local recurrence and an increasing reluctance to prescribe postoperative conventional fractionated radiotherapy, the perioperative radiosurgical treatment of brain metastases is increasingly discussed. The question whether treatment results differ between pre-operative and post-operative SRS was analysed based on comparison of 209 patients who underwent post-operative SRS with 17 patients with pre-operative SRS. The median survival times after treatment were 9.8 months in post-operative SRS and 10.3 in pre-operative SRS. The two groups did not differ significantly in cumulative incidences of neurological death, local recurrence, neurological deterioration, remote recurrence and re-SRS. However, the crude rate of subdural seeding in pre-operative SRS (5.9%) was significantly lower than that in post-operative SRS (31.1%, p=0.03), but this difference was not shown to be statistically significant using the competing risk analysis (p=0.07).

The suspicion of an increased leptomeningeal seeding after surgical removal of brain metastases was confirmed by another study of 330 patients with a minimum follow-up of 3 months with no prior whole brain radiation or stereotactic radiosurgery who had been treated for brain metastases with Gamma Knife. The 3-year Kaplan-Meier estimate for development of meningeal spread was 19% for those patients who underwent prior surgery vs. 8% for those who did not (p=0.02). On multivariate analysis of primary histology and prior surgical resection, only prior surgical resection remained predictive of meningeal spread (p=0.02).

The question if the previous surgical resection improves the outcome, was studied in a matched-pair analysis was performed in 90 patients who underwent resection followed by radiosurgery to the tumor bed (SURG+SRS) who were matched (1:1) with patients who underwent SRS alone (Gamma Knife or CyberKnife, follow-up ≥3 months and KPS score of ≥70). Patients were matched according to age, tumor size, and histology. Local control was not statistically different between the two groups (87% for SURG+SRS and 71% for SRS alone). Similarly, regional CNS control and overall survival were not different. However, the rate of radiation necrosis was higher in SURG+SRS compared with SRS alone, 22% vs. 4% respectively (p=0.003). The conclusion was that surgery followed by SRS to the tumor bed did not improve local control or survival compared to SRS alone but did increase the risk of radiation necrosis.

When GKRS is applied to the resection cavity (n=76) without prior WBRT (median 16 Gy, median volume 8.6 cc), a crude failure rate of 25% was shown. The 1-year local control for treatment volume over 10 cc was 64% versus 82% for treatment volume under 10 cc (p = 0.059). A similar local tumor control rate of ca 75% after Gamma Knife radiosurgery to the postoperative resection cavity was shown in another study: (Data from presented slides) (n=118; mean cavity volume 13 cc, average marginal dose 18 Gy). It was interesting that margin dose > 16 Gy yields better local control and increasing delay between surgery and SRS increased recurrence.
Multiple Metastases

Among the very relevant data presented at the meeting were the results from the Japanese multi-institutional retrospective cohort study that showed that patient survival was independent of number of brain metastases. Similarly, the group had previously shown in a Japanese multicenter study with 1194 patients (JLGK0901) that stereotactic radiosurgery without WBRT in patients with 5-10 brain metastases is non-inferior to radiosurgery in patients with 2-4 brain metastases. Overall survival did not differ between the patients with 2-4 tumours and those with 5-10 metastases. The proportion of patients who had one or more treatment-related adverse event of any grade did not differ significantly between the two groups of patients with multiple tumours.

The conclusion of the study presented at the Gamma Knife Society Meeting was that patients with 10 or more brain metastases are not unfavorable candidates for a treatment with stereotactic radiosurgery alone. A case-matched study was conducted using the propensity score matching method with 720 selected patients. Patients with 2-9 brain metastases were compared to patients with 10 and more brain metastases. There was no significant difference in post-SRS median survival times between the cohorts, incidences of neurological death were very similar, with no significant difference in neurological survival, neurological deterioration or SRS-related complications. The conclusion was that treatment results after radiosurgery were not inferior in patients with 10 or more brain metastases as compared to patients with 2-9 brain metastases.

Survival times were significantly longer following Gamma Knife radiosurgery (GKRS) compared to fractionated whole brain radiotherapy (WBRT) in retrospective study of 866 patients with ≥3 brain metastases (6.4 vs. 2.4 months, p<0.0001). There was no significant difference in survival times between 3-4 and >4 BM neither following GKS nor following WBRT confirming that the number of brain metastases had no predictive power. Patient selection, longer survival among the more recently treated patients and better local tumor control following GKS are all factors that may have contributed to this difference.

Metastases Grading Scales

The diagnosis-specific Graded Prognostic Assessment (DS-GPA) is a prognostic index for patients with brain metastases. A multi-institutional retrospective database of 3940 patients from 11 institutions was analyzed using univariate and multivariate analyses to identify prognostic factors associated with outcomes by primary site and treatment. Significant prognostic factors were used to define the DS-GPA prognostic indices. A GPA of 4.0 correlates with the best prognosis and 0.0, the worst. According to this analysis, significant prognostic factors varied by diagnosis:

- For lung cancer, prognostic factors were Karnofsky performance status (KPS), age, presence of extracranial metastases, and number of brain metastases.
- For melanoma and renal cell cancer, prognostic factors were KPS and the number of brain metastases.
- For breast cancer, prognostic factors were tumor subtype, performance status and age.
- For gastrointestinal cancer, the only prognostic factor was the KPS.

The validity of the DS-GPA was then tested in an independent Japanese study of 179 patients with brain metastasis from breast cancer undergoing Gamma Knife radiosurgery. The conclusion in this series was that DS-GPA appeared to not be applicable, since the only significant difference was found between groups 2 and 3. Another study tested the validity of 6 grading systems in patients undergoing Gamma Knife radiosurgery in 2645 patients with brain metastases. The grading systems were the original recursive partitioning analysis (RPA, Gaspar, 1997), score index for stereotactic radiosurgery (SIR, Weltman, 2000), basic score for brain metastases (BSBM, Lorenzoni, 2004), modified-RPA (m-RPA, Yamato, 2013), qualitative survival score (QSS, Serizawa, 2013) and diagnosis-specific graded prognostic assessment (DS-GPA, Sperduto, 2011). The authors concluded that BSBM and QSS appeared to be good, while DS-GPA was less applicable to brain metastasis patients treated with GKS than the other systems. According to this evaluation, SIR and m-RPA appear to be the most useful grad-
ing systems for all cancer types and showed highly statistically significant differences for overall survival\(^3\). Another group tested the validity of 4 grading systems (RPA, SIR, BSBM, GPA) in 389 evaluable patients confirming the usefulness of all 4 systems of classification to be used to select patients for radiosurgery. The BSBM score and the GPA model were seen to be as powerful as the RPA and SIR systems. BSBM and SIR scores remain significant after a multivariate backward elimination\(^3\). The validity of grading scales in the specific situation of a radiosurgical retreatment was specifically tested based on 746 patients from the Japanese prospectively accumulated database. RPA, SIR, BSBM and the Modified RPA showed statistically significant differences in median survival time with no or minimal overlapping of 95% confidence intervals between any two pairs of groups. Differences between the GPA 3.5 - 4.0 and GPA 3.0 groups however, did not reach statistical significance\(^4\).

Since classical indices rather predict survival than neurological outcome, Toru Serizawa proposed the modified BSBM (m-BSBM) by adding 4 brain factors to the original BSBM. The conclusion after verification in 2645 patients was that the new index appeared to be excellent for predicting both qualitative survival and neurological survival\(^5\).

Metastases and Adverse Radiation Effects

The tumor volume is the primary limiting factor in radiosurgery since 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 steroid medication and in rare cases a surgical intervention. Adverse radiation effects are generally seen in larger metastases or uncontrolled treatments and are uncommon when metastases smaller than 2.5 cm are treated. A detailed dose/volume analysis was carried out and was related to the MRI follow-up in 124 patients surviving more than 9 months with 173 metastases larger than 10 mm. There were adverse radiation effects in 20.2% and local recurrences in 11.6%. As an objective representation of the prescribed dose, the dose given to 95% of the volume (V95) was measured, which according to logistic regression is a significant factor for recurrence. The conclusion is that the number of adverse radiation effects can be further reduced, when dose/volume relations are taken into consideration. The dose given to 95% of the volume (V95) and ratio between V10Gy and tumor volume (KARE factor) serve as an empirical algorithm for the approximation for the ideal dose range in the Gamma Knife treatment of brain metastases avoiding both adverse radiation effects and local recurrences\(^6\). Another study analysed clinical parameters as predictors of dexamethasone use after stereotactic radiosurgery in a retrospective analysis of 162 patients with brain metastases (on a multivariable model). Dose volume relations were not taken into consideration. 29% of patients had steroid use post-SRS. Patients not requiring steroids or with decrease in steroid use after radiosurgery were more likely to be male, \(\geq\)56 years old, with smaller tumors (<2.0 cm), have no brain mets at initial diagnosis, and had controlled EDS\(^7\). Despite anecdotal evidence that treatment related imaging changes may be greater after immunotherapy, there was no statistically significant association between treatment with traditional chemotherapy, immunotherapy, or targeted therapy and development of radiation necrosis\(^8\).
Post-Treatment Imaging PET

Imaging during follow-up is essential to differentiate between uncomplicated cases, adverse radiation effects and recurrences. Unfortunately, standard MRI is insufficient for this differentiation. Alternatively, $^{11}$C-Methionine proved useful for differential diagnosis between radiation injury and recurrence. The negative predictability on tumor recurrence in $[^{11}C]$methionine PET-CT was 85.7% in a small series, and the positive predictability 77.4%47. Similarly, another series showed that the sensitivity and specificity for radiation injury in Methionine-PET was 87.0% and 71.4%, respectively. The lesion that accumulated FDG had an 88.9% possibility of recurrence48.

Treatment of Adverse Radiation Effects: Bevacizumab

The standard treatment for radiation induced edema and adverse radiation effects is a steroid medication with all its well known side effects during long-term administration. As an alternative, Bevacizumab has been suggested as a new treatment modality for adverse radiation effects due to its ability to block the effects of vascular endothelial growth factor (VEGF) in leakage-prone capillaries. In a small series of 10 patients where Bevacizumab was used in otherwise poorly controlled symptomatic adverse radiation effects (5 mg/kg 2-3-week interval; administered over 90 minutes), MRI analysis revealed an average reduction (of edema) 48.3% in T2-weighted images (data from slides) and Dexamethasone reduction in all patients with significant clinical improvements in 90%.49

Successful treatment of adverse radiation effects with Bevacizumab. From Tang Xuqun49
**Targeted Therapy and Radiosurgery**

Erlotinib is a reversible tyrosine kinase inhibitor acting on the epidermal growth factor receptor (EGFR), similar to Gefitinib (Iressa), which was the first drug of this type. It was shown that Erlotinib was well tolerated in combination with WBRT for the treatment of brain metastases with response rates up to 86%\(^5\). Similarly, Lapatinib is a tyrosine kinase inhibitor that interferes with the HER2/NEU and EGFR pathways and is used in HER2-positive breast cancer. In patients with brain metastases, objective CNS responses have been described in 65.9%\(^5\). Ipilimumab is a monoclonal antibody that targets CTLA-4, which is expressed on a subset of activated T-cells as a negative regulator of T-cell activation. Blockade of CTLA-4 potentiates an antitumor immune response and leads to tumor regression\(^5\). The use of 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%\(^3\). Ipilimumab is the first agent to show overall survival benefit in patients with advanced melanoma\(^5\). Approximately 50% of patients with cutaneous melanoma have a mutation in BRAF kinase, leading to constitutive activation of the mitogen-activated protein kinase pathway and unregulated cell growth. Selective inhibitors of the mutated BRAF kinase produce response rates of approximately 50% and recently the BRAF inhibitor Dabrafenib was approved for use in patients with metastatic melanoma\(^4\). These new compounds for targeted chemotherapy provide an obviously novel and highly effective approach in cancer patients and stereotactic radiosurgery offers the technology for a corresponding effect against brain metastases. The combination of these therapeutic approaches promises a prognostic break-through in selected oncological patients\(^5\).

**Lung Cancer**

In 817 patients with NSCLC treated by GKRS median overall survival from diagnosis of brain metastasis was 68.8 weeks. Patients with EGFR or ALK mutation had a better prognosis\(^5\). Similar results were seen in 757 patients undergoing GKRS with a median survival time of 12.8 months (range 0.7-166) from the diagnosis of brain metastasis and a local tumor control rate of 92.5%. Survival time after SRS was decreased in patients treated with prior whole brain radiation (median 7.5 months) compared to SRS alone (median 10.2 months)\((p=0.006)\). A more negative prognosis was described in patients with squamous cell carcinoma when compared to adenocarcinoma\(^5\).

In brain metastases of small cell lung cancer the established treatment is the use of WBRT, but it has been shown previously that Gamma Knife appears to be as effective in SCLC as in NSCLC\(^5, 6\). A study was presented after radiosurgery of (less than 10) SCLC brain metastases \((n=41, 79\% \text{ evaluated})\), the 12-month rates of local control failure was 14% and the median survival time 8.1 months\(^6\).

In 1999, the World Health Organization categorized large cell endocrine carcinoma (LCNEC) as a variant of large cell carcinoma. Although LCNEC of the lung is categorized among NSCLC, the biological behavior of LCNEC tumors is very similar to that of small cell lung carcinomas. In 18 patients treated GKRS, the overall median survival for patients with brain metastases from LCNEC of the lung was 12.6 months. Local tumor control was achieved in all 15 patients with imaging follow-up\(^6\).
**Iressa (Gefitinib™)**

The outcome of patients with brain metastases from non-small cell lung cancer treated either by WBRT followed by GK, or by IRESSA, or by the combination of GK and IRESSA was evaluated based on the records from the National Health Insurance Research Database of Taiwan. WBRT was the first line treatment for nearly all patients. Of the 60,194 patients with newly diagnosed NSCLC, 23,874 (39.6%) developed brain metastases. The median survival after the diagnosis of brain metastases was 0.53 years for WBRT, 1.01 years for WBRT+IRESSA, 1.46 years for WBRT+GKRS and 2.25 years for WBRT+IRESSA+GKRS, respectively (p<0.0001) showing extended survival for patients receiving GKRS or IRESSA. Results from a smaller retrospective analysis of 161 patients (from slide) did not support the conclusion of the previous analysis: There was no significant difference in overall survival rates after application of Gefitinib or Erlotinib alone or in combination with WBRT or GKRS. Because Temozolomide (TMZ) and Erlotinib (ETN) cross the blood brain barrier and have documented activity in NSCLC, a phase III study was designed to test whether these drugs would improve the OS associated with WBRT+SRS. 126 patients with NSCLC (1-3 BM) were randomized and showed qualitatively different median survival times (13.4 mo for WBRT+SRS, 6.3 mo for WBRT+SRS+TMZ and 6.1 months for WBRT+SRS+ETN), although the differences were not statistically significant. Performance status at 6 months was better in the WBRT+SRS arm. Because the analysis was underpowered, these data suggest but do not prove that increased toxicity was the cause of inferior survival in the drug arms. So far neither this, nor any other phase III randomized controlled trial, has shown chemotherapy improves survival for patients with brain metastases.

**Melanoma**

In patients with brain metastases from malignant melanoma treated with GKRS (n=102; mean tumor volume 6.0 cm³, prescription dose 20 Gy; range: 15-24), local control was achieved in 94% and the median overall survival was 6.4 months from the radiosurgical treatment and 53.0 months from the diagnosis of the primary melanoma. Intratumoral hemorrhage was seen in 11% and adverse radiation effects in 9%, but rates for tumor hemorrhage appeared to be similar before and after radiosurgery (data from slides).

**Breast Cancer**

In GKRS for brain metastases from breast cancer (n=90), use of anti-HER2 targeting agents, volume ≤1.2cc, and prescribed dosage ≥18Gy were predictive factors for local tumor control (according to slides).
Colorectal Cancer

In patients with brain metastases from colorectal carcinoma treated with GKRS (n=51; mean tumor volume 5.2 cm³ (range, 0.01-45.5 cm³), mean prescription dose 19.4 Gy, range, 5-23 Gy), the actuarial local tumor control rates were 78.6% and 72.9% at 6 and 12 months after GKRS, respectively. Median overall survival time after GKRS was 11.0 months.68 Another series showed a comparatively short median short survival of 4.3 months (range, 0.2-26.5 months) in patients with brain metastases from colorectal carcinoma (n=188; median prescription dose 18 Gy: range: 10-25 Gy).69

Other Primary Cancer Types

Hepatomas are rare (but in Korea the 4th common primary tumor in men) and rarely metastasizes to the brain. These tumors are usually diagnosed with intratumoral bleeding. In patients with brain metastases from hepatoma treated with GKRS, tumor growth was controlled in 79.6% (cited from slide) (followed n=49/73; mean volume 7348 mm³, range: 187-33700 mm³, prescription dose 23.2 Gy, range: 15-32)70.

In patients with brain metastases from esophageal carcinoma treated with GKRS, the median survival time from the diagnosis of brain metastasis was 8 months and median survival from SRS was 4.2 months, corresponding to a 6-month survival of 45% and a 12-month survival of 19% after SRS (n=26; mean tumor volume 5.7 cm³, range 0.5-44 cm³, prescription dose 17 Gy: range: 12-20Gy)71.

In patients with brain metastases from hepatocellular carcinoma treated with GKRS, the median overall survival time after GKS was 5.0 months (n=14; mean tumor volume 8.16 cm³, mean prescription dose 18.7 Gy)72.

Cost and Reimbursement

Cost containment is an essential issue in healthcare, and treatment methods that are based on outpatient procedures or short-term hospitalizations are gaining momentum in the current environment of decreasing ward capacity. Neurosurgery is a good example of this development, with a striking trend towards minimally invasive methods. The widespread implementation of Gamma Knife radiosurgery has started to replace previously invasive resections of AVM, skull base tumors, acoustic neuromas and brain metastases. While cost considerations may not directly influence individual treatment decisions, economic comparisons can be highly relevant in the regional determination of ward capacity. Treatment options are also validated according to economic standards.

In a comparison of costs, 40 patients were treated with LINAC-based SRS and 61 patients were treated with the Leksell Gamma Knife Perfexion. In unadjusted analysis, there was a small not statistically significant difference in median overall survival between the Gamma Knife and LINAC-based radiosurgery groups in favor of the Gamma Knife (12 months vs. 7.8 months respectively, p<0.01). The cost associated with actual SRS delivery was higher for Gamma Knife (incremental cost difference of $11,058 per patient, p<0.001). However, Gamma Knife SRS was associated with lower periprocedural costs than LINAC-based SRS ($8832 vs. $14934, p=0.002), as well as lower lifetime costs ($100,961.70 vs $173,429.30 per life-year saved, p=0.04). The cost-effectiveness of Gamma Knife was enhanced as the number of lesions treated rose. The conclusion of the study was that Gamma Knife radiosurgery was associated with better cost-effectiveness than LINAC-based SRS with a cost-savings of approximately $70,000 per life-year saved73.
In another analysis, treatment costs in 289 patients with brain metastases were computed from a Medicare payer perspective including initial and salvage therapies for brain metastases, hospitalizations, management of complications, and imaging. Average treatment cost and average cost per month median survival were compared between SRS alone, SRS+W-BRT, or Surgery + SRS. The overall survival was not significantly different with median survivals of 9.8 months, 7.4 months, and 10.6 months, respectively. Despite an increased need for salvage therapy, the average cost per month median survival was $2,382/month for SRS alone, $3,106/month for SRS+W-BRT, and $4,380/month for Surgery+SRS (p=0.004). SRS alone had an incremental cost-effectiveness ratio of $181 per month improvement in overall survival. The conclusion was that patients with brain metastases initially treated with stereotactic radiosurgery alone, received more cost-effective care than SRS+W-BRT despite an increased need for salvage therapy.\textsuperscript{74}
The overall bleeding rate was 2.25% (mean volume 8,957 cm³, mean marginal dose 21.4 Gy, mean follow-up 41.8 months)\textsuperscript{76}. In another study of 97 AVM patients treated with GKRS, MRI showed the AVM occlusion in 64% (mean nidus volume 2.71cc, mean prescription dose 22.5Gy)\textsuperscript{77}.

When MR criteria were applied to document the treatment effect, the obliteration rate was reported to be 94% and hence unusually high (n=99, median volume 6.25 cm³, median prescription dose 21 Gy)\textsuperscript{78}.

Even for highly eloquent locations such as the post-geniculate visual pathway, it was shown that 82% of patients receiving 22 Gy or greater had complete obliteration, and GKRS provided an effective treatment with a relatively high rate of visual field preservation (n=171; median target volume 6.0 cm³; median prescription dose 19 Gy)\textsuperscript{79}. AVMs with a volume <5 cm³ had an obliteration rate of 60% at 3 years and 79% at 4 years. The actuarial rates of visual deficit were 3% at 3 years, 5% at 5 years and 8% at 10 years. The annual hemorrhage rate during the latency interval was 2% and no hemorrhages occurred after confirmed obliteration\textsuperscript{79}. In periventricular AVM (n=188), the actuarial rates of total obliteration were 32% at 3 years, 55% at 4 years, 60% at 5 years, and 64% at 10-years. Permanent neurological deficits due to adverse radiation effects (ARE) developed in 4%. 13% sustained a hemorrhage during the initial latency interval after SRS indicating an annual hemorrhage rate of 3.4% prior to obliteration\textsuperscript{80}.

When arterial aneurysms coexist together with AVM, combined management should be considered. Many of these aneurysms are treated with embolization combined with GKRS for an AVM. In a series of 10 associated aneurysms that had remained untreated after GKRS, 4 intranidal aneurysms and 4 flow-related distal aneurysms regressed completely; 2 flow-unrelated aneurysms were not changed in size\textsuperscript{81}.

### Vascular Malformations

#### AVM: General Outcome

In a larger retrospective analysis of 401 patients with AVMs who were treated with GKRS, the overall angiographic obliteration rate was 77.2%, and was 88.8%, 59.7%, and 22% for small, medium and large AVMs.

![Graph showing cumulative numbers of arteriovenous malformations worldwide from 1991 to 2013.](image-url)

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Unruptured Cerebral Arteriovenous Malformations

The necessity to treat unruptured AVM has been questioned in particular with regard to the ARUBA study\(^8\) as discussed in great detail by Gary Steinberg\(^9\). It was emphasized that the very short follow-up period of the ARUBA study is a serious issue which caused criticism raising the question as to whether any preliminary result of the study can be evaluated at all at this early time point. The unusually and unacceptably high complication rate in the interventional arm is another unclear issue\(^8\). In this context, the presented retrospective study of Gamma Knife SRS in 276 patients with unruptured AVMs is important (median follow-up: 49 mo, median nidus volume 4.4 cm\(^3\)). The rates of obliteration were 64%, 80% and 88% at 3, 5 and 7 years, respectively. Permanent adverse effects were observed in 2.9%. The annual hemorrhage rates after SRS were 0.84% during the latency interval, which decreased to 0.29% after obliteration. Deep venous drainage was the only factor associated with hemorrhage after SRS\(^8\).

Large AVM

It is well known that large AVM have a reduced chance of obliteration and increased risk for side effects after single session radiosurgery. Consequently, it was shown that giant AVMs which had been treated with Gamma Knife showed a complete obliteration rate of only 36%, and a subtotal obliteration (>70%) of 36% and partial obliteration of 28%. (n=11, mean AVM volume 41 cc, mean prescription dose 14.2 Gy)\(^8\). Similarly, in pediatric AVM with volumes >10cc, the obliteration rate after single treatments was only 25% with high risk for permanent complications in 37% and bleeding in the latency period (data from slide)\(^9\).
The alternative is volume- or dose-staged radiosurgery. In 63 patients with large AVM (>10 mL) treated with volume-staged stereotactic radiosurgery (VS-SRS), decreasing treatment volume per stage allowed higher dose per fraction without increasing complications. With reduction of the treated median volume per stage from 15 to 6.8 mL and increase of the median dose from 15.5 Gy to 17 Gy, the rates of near-obliteration were increased from 24% to 42% (p=0.0001). The conclusion was that patients with large AVM should be considered for VS-SRS and be treated with doses of at least 17 Gy.

Other preliminary results in a small study may suggest that staged dose radiosurgery provides more promising results in terms of obliteration than staged volume radiosurgery in large AVMs (volume >15 cc). (data from slides) (mean AVM volume 15.8 cc, mean prescription dose 14.5 Gy).

Pediatric and Adolescent Patients

High rates of complete obliteration and very low frequency of permanent morbidity or severe bleedings during the latency period encouraged widespread application of radiosurgery in pediatric and adolescent patients affected with cerebral AVMs. A retrospective series which studied the outcome of GKRS in a series of 100 pediatric and adolescent patients with AVMs, demonstrated that angiographically documented actuarial cAVM obliteration rates were 73% and 86% at 3- and 5-years, respectively (mean cAVM volume 4.99 cc; prescription dose 19.8 Gy). Permanent symptomatic GK-related complications were observed in 6% of cases with surgical removal of post-radiosurgical imaging change needed in 3 cases. Hemorrhage during the latency period occurred in 8% of patients. Very similar results were reported in another study of Gamma Knife radiosurgery in 75 children with AVM, where nidus obliteration was achieved in 81% with marginal dose > 20 Gy being a favorable factor for obliteration (median target volume was 1.9 cm³; median prescription dose 20 Gy). Actuarial obliteration rates at 3 and 5 years after SRS were 70% and 87%, respectively and 4% developed treatment related neurological deterioration (median 9 months). Annual bleeding rate after SRS was calculated as 0.3%.

Treatments of AVMs During Pregnancy

The risk of hemorrhage in patients who become pregnant during the latency interval following GKRS for AVMs was evaluated in 253 women of childbearing age with 828.7 patient-years of follow-up. The data showed that pregnancy appears to be a risk factor for AVM bleeding. Prior to obliteration, twenty hemorrhages occurred in non-pregnant patients equating to an annual hemorrhage rate of 2.5% for non-pregnant women in the latency interval. Eighteen pregnancies occurred and two patients had hemorrhages, yielding an annual hemorrhage rate of 11.1% for women who became pregnant in the latency interval after SRS.

AVM Adverse Radiation Effects

In a large retrospective series of 1426 GKRS procedures performed for AVMs at the University of Virginia, a total of 33.8% of nidi developed radiation-induced imaging changes, in 19.7% classified as Grade I, in 11.5% as Grade II, and in 2.6% as Grade III. The median duration from GKS to the development of radiation-induced imaging changes was 13 months (range 2-124 months). The overall incidence of symptomatic imaging changes was 8.6%. The focus of a series from the University of Pittsburgh were the associated symptoms and symptomatic adverse radiation effects that were described in 6% of 879 patients treated for AVM with GKRS (median target volume 3.4 cc, median margin dose 20 Gy). Overall rates of symptomatic ARE were 2.7% at 1 year, 5.1% at 2 years, 6.0% at 3 years, and 6.9% at 5 years and rates of permanent symptomatic ARE were 0.7% at 1 year, 1.8% at 2 years, 1.9% at 3 years, and 2.7% at 5 years. Among 817 patients, 23 were identified who had developed late cysts after GKRS for AVM. Cyst formation was detected from 1.1 to 16 years (mean 5.4 years) after GKS. Histological examination in 14 cases showed dilated capillary vessels with wall damage such as hyalinization and fibrinoid necrosis, marked protein exudation, and hemorrhage.
Cavernous Malformations

Currently there are three options for cavernous malformations: operative resection, radiosurgery or no active treatment at all. As one of the earlier analyses of radiosurgery for cavernous malformation, Kondziolka et al published two studies where initially the natural history of cavernous malformation was defined\(^9\): In patients without a prior bleed, the prospective annual rate of hemorrhage rate was 0.6% and patients with prior hemorrhage had an annual bleed rate of 4.5%. The same group in Pittsburgh demonstrated elegantly that the proportion of patients with hemorrhage after radiosurgery was significantly reduced, but in the first 2 years after radiosurgery, an annual hemorrhage rate of 12.3% per year was still found. Only in the 2- to 12-year interval after radiosurgery, the annual bleeding rate decreased to 0.76% per year\(^9\).

In cavernous malformations it is important to differentiate between annual bleeding risk in randomly found cavernous malformations and the rebleeding risk for cavernous malformations that have bled before. Furthermore the bleeding risk per patient should be differentiated from bleeding risk per lesion before and after treatment. A specific example from a recent paper shows an annual bleeding rate of 2.9% until the first hemorrhage, and an annual risk for rebleeding of 30.5% until treatment. Within 2 years after radiosurgery there was a reduced rebleed risk of 15%, which fell to 2.4% per patient year thereafter\(^7\).

The provided radiosurgical data are generally interpreted as evidence for a reduced risk for rebleeding after initial hemorrhages, whereas it appears difficult to find arguments that a treatment-induced significant improvement actually occurs in incidental cavernous malformations.

A presented study of cavernous malformations analysed the outcome after conservative treatment or surgery, showing an annual rate of hemorrhage until the first event from of 1.7 and 1.8% respectively. Rebleedings occurred in many cases of conservative group, whose annual rate of hemorrhage was 10.2% per year after the first event, 19.7% after the 2nd event. In surgery group, the rate was only 1.9% per year after 1st event, and 2.7% per year after the surgery for cavernous malformations\(^9\).

In a joint retrospective study 334 cases of cavernous malformation were collected from 23 Gamma Knife centers all over Japan (mean lesion size: 14.8 mm, mean marginal dose: 14.6 Gy). A dose dependent response was confirmed with more frequent complications occurring at a marginal dose over 15 Gy, and in cavernous malformation with more than 15 mm in diameter. The rates of annual hemorrhage were estimated to be 6.7% during first 2 years after radiosurgery and 3.3% thereafter. Rebleeding rates appeared to be lower at prescription doses of >15 Gy; differences however, were not statistically significant\(^9\).

![Statistically insignificant correlation between rebleeding and dose in Gamma Knife treatment of cavernous malformations; From Yoshihisa Kida \(^9\)](image)

Very similar bleeding rates after Gamma Knife were reported in another study where the authors reported 92 symptomatic patients with brainstem cavernous malformations who were treated microsurgically (n = 43) or radiosurgically (n = 49) at a median margin dose of 12 Gy (6-16 Gy). In the first two years after GKRS the hemorrhage rate was 2.6% but dropped to 0.6% after the first two years. It was notable, that for surgically treated patients with residual lesions the annual postoperative hemorrhage rate was 8.8%\(^10\).
In certain anatomical locations the complete surgical removal of meningiomas can be associated with a major postoperative neurological deficit. Hence, the consequence of the close involvement of relevant and sensible structures is an incomplete tumor resection in order to preserve the neurological function. Long term follow-up studies have demonstrated that incompletely resected skull base meningiomas carry a significant risk for symptomatic recurrences. Gamma Knife radiosurgery has an important role to complete microsurgery in these cases through provision of a postoperative long-term tumor control.

Under the auspices of the European Gamma Knife Society (EGKS), a retrospective observational analysis of 4565 consecutive patients harboring 5300 benign meningiomas was performed by 15 participating centers. All patients were treated with Gamma Knife radiosurgery (median tumor volume 4.8 cm³, median prescription dose 14 Gy, median imaging follow-up was 63 months). Detailed results from 3768 meningiomas (71%) were analyzed. The volume of treated tumors decreased in 58%, remained unchanged in 34.5%, and increased in 7.5%, thus providing a control rate of 92.5%. Five- 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, for female vs male patients, for sporadic vs multiple meningiomas, and for skull base vs convexity tumors. Permanent morbidity rate was 6.6% at the last follow-up.[10] In a group of 722 patients, it was shown that the relative risk for an aggravation of a peritumoral edema after GKS was 4.58 times higher when a meningioma presented with peritumoral edema.
at the time of radiosurgery when deterioration can be expected in 60%. In the group of meningioma without initial peritumoral swelling, the edema occurred in 13.1%\textsuperscript{107}. A higher rate of side effects was described in a smaller retrospective analysis showing that 18.7% developed new T2 signal change suggestive of edema with 10.8% being symptomatic with headache, fatigue or ataxia (data from slides). (75 followed out of 170 treated patients, median follow-up 36.2 months, average tumor volume 5.2 cm\textsuperscript{3})\textsuperscript{108}.

The dural tail (DT) has been described as a common feature in meningiomas. The necessity to include the dural tail in Gamma Knife radiosurgery is still a matter of debate. Gamma Knife radiosurgery was performed in 471 meningiomas with dural tails in 209 (44%) tumors (median prescribed dose of 13 Gy, median follow-up 48 months). Only the part of the dural tail closely related to the tumor mass was included in the target definition. Since no tumor growth was found outside the target in the dural tail during the median follow-up up 48 months, the conclusion was made that is not necessary to include the entire dural tail of meningiomas in Gamma Knife radiosurgery\textsuperscript{109}.

Long Term Follow-Up

With regard to the very slow growth rate of meningioma, however, it is essential to provide long-term data in order to be able to predict the outcome with regard to local control, remote control and potential late side effects. So far, only very few published studies had followed meningioma patients for more than 5 years after radiosurgical treatment. As one of the longest available follow-up investigations of patients with meningiomas, 86 patients have been followed after treatment with Gamma Knife radiosurgery with a median follow-up period of 10 years documenting a persistent high local tumor control, which was only slightly lower than in other published observations with shorter follow-up. Tumor control was achieved in 87.8% of meningiomas. For the follow-up potential very long latencies to recurrences have to be taken into consideration; the median time between initial treatment and recurrence was 5.8 years and out of field recurrences were documented at a median of 7.5 years in 15.1% of patients. Meningiomas treated with a prescription dose of >13.4 Gy experienced a significantly lower rate of local recurrences (7.1% vs 24% p=0.0096)\textsuperscript{110}.

Hypofractionation

In larger meningiomas, the treatment alternatives are either a partial tumor resection and adjuvant Gamma Knife radiosurgery or the recently applied hypofractionated stereotactic radiosurgical treatment. In 42 patients with meningiomas who underwent fractionated Gamma Knife radiosurgery, the local control rate of tumor was 97.2% and the symptomatic control was 94.4%. Median dose of 6 Gy was delivered over median of 2.7 fractions (median tumor volume 15.2 ml, range: 2.1-53.2 ml, median follow-up up 32.8 months). Tumor volume decreased (>25%) in 22.2%, remained stable in 75%, and increased (>25%) in 2.8%\textsuperscript{111}. Similarly, in perioptic meningioma, the established threshold doses for optic nerves may not allow effective single session treatments which require prescription doses >14 Gy. The alternative is a multi-session radiosurgery with Gamma Knife which appeared to be safe in a series of 97 patients with perioptic meningioma immediately adjacent to the anterior visual pathway (mean tumor volume was 8.28 cc (range 0.33-34.2 cc, mean follow-up 26.4 months). Gamma Knife radiosurgery was delivered in three sessions with a mean prescription dose of 6.8 Gy per session (range 6-7 Gy) and a mean total prescription dose of 20.4 Gy (range 18-21 Gy). Maximum dose to the optic apparatus was always below 7 Gy for each session. At last follow-up, tumor volume was unchanged in 50.5%, decreased in 47.4% and increased in 3.1%. 5.4% developed new cranial nerves palsies following GKS, 35.1% had an improvement of previous palsies. Among all patients with visual deficits at GKS 23.8% had an improvement while it worsened in 2.4%\textsuperscript{112}.
In vestibular schwannoma, Gamma Knife is highly effective in stopping potential tumor growth while preserving normal facial function and hearing. The goal of every acoustic neuroma management is to provide the best outcome with the lowest possible risk level. The long-term results after Gamma Knife treatment is comparable and often even superior to the best results with open microsurgical techniques. The functional results after Gamma Knife are significantly superior to conventional surgical results. Average tumor control >95% is reported in the majority of published series.

A review of 23 articles representing 2204 patients revealed an overall facial nerve preservation rate of 96.2% after Gamma Knife and a review of 45 articles representing 4234 patients showed an overall hearing preservation rate of 51% after radiosurgery.

A recent study compared the outcome after treatment of acoustic neuroma with open surgical resection or Gamma Knife. The mean hospital stay was 2.5 days (2–5 days) in the Gamma Knife group and 12.5 days (10–30 days) in the surgery group. Hearing was preserved in 17 out of 28 patients with functional hearing 2 years after Gamma Knife treatment, while hearing could not be preserved in any patient after open surgical resection.

A large group of patients was presented who had undergone GKRS as primary treatment for vestibular schwannoma. The main limitation of the present study was that a detailed radiological follow-up was only available in 60.7% (210/346) and audiometrical follow-up in 41.3% (143/346). Tumor control was achieved in 97.1% of followed patients. Overall functional hearing preservation rate at long-term follow-up was 47.5%; in GR 1 patients, this value increased to 72.2% (median tumor volume 1.2cc, range 0.014-14.3 cc; median prescription dose 13 Gy).
To clarify the appropriate length of follow-up after GKRS, a presented series analyzed changes in MRI and clinical status more than 10 years after the treatment in 80 patients with unilateral vestibular schwannomas. Despite initial marked tumor response for more than 10 years after GKRS, surgical removal was necessary in 3.8% (3/80) at 143, 151 and 167 months. No new cranial nerve symptom without tumor growth and no malignant transformation of the tumor were observed more than 10 years after GKRS117.

Tumor volume is considered as the main limitation for single session radiosurgery. Hence it is essential to define the specific maximum doses and volume for a safe treatment. 90 patients with large vestibular schwannomas (>25 mm) treated with GKRS, showed significant tumor volume reduction in 87.8% and overall tumor control in 94.5% (mean tumor volume 5.98 cc, median prescription dose 13 Gy, mean follow-up period 67.9 months). Eleven patients developed hydrocephalus at follow-up requiring a ventriculo-peritoneal shunt. The conclusion was that Gamma Knife radiosurgery is a safe and effective treatment even for larger vestibular schwannomas118.
Hearing Preservation and Threshold Doses

The doses applied to the cochlea could have a potential impact on hearing deterioration after GKRS. Actuarial incidences of hearing preservation were 51% and 26% at the 60th and 120th post-SRS months. Mean cochlear dose higher than 4.2 Gy and maximum cochlear dose higher than 6.9 Gy were significantly associated with post-SRS hearing worsening. Age and tumor size were further factors (n=131, median tumor volume 2cc, prescription dose 12 Gy)\textsuperscript{119}. The outcome after low-dose GKRS was described in retrospective study of unilateral vestibular schwannoma that showed that tumor control rate was not significantly related to radiation doses (\geq 12 Gy vs. \geq 11 Gy vs. <11 Gy). The conclusion was that Gamma Knife radiosurgery achieved high percentage of tumor control and good hearing preservation even when doses of less than 12 Gy were applied (105 patients, mean follow-up 76 months, median tumor volume 5.05 cc, median tumor dose 11.4 Gy)\textsuperscript{120}. This result is potentially important with regard to a study that showed in a multivariate analysis, that patients receiving a marginal dose of \geq 12 Gy were over 7 times more likely to develop non-serviceable hearing\textsuperscript{31}. Tumor marginal dose \geq 12 Gy and cochlea max dose were jointly significantly associated with the development of non-serviceable hearing\textsuperscript{121}. But even more relevant, patients with a pretreatment speech discrimination score (SDS) of \geq 70% were 11.1 times less likely to develop non-serviceable hearing following SRS. In this study neither mean cochlear dose nor modiolar point dose were associated with hearing preservation at any threshold\textsuperscript{121}. Similar results were shown in a prospectively analyzed series of 94 patients with vestibular schwannoma treated with GKRS where patients in GR class 1 & 2 retained serviceable hearing in 67.2% of the cases. The mean maximal dose received by the cochlea in patients in GR class 1 and 2 was 4.2 Gy. Among the patients with a follow-up of at least one year, those with Koos I tumors had the highest probability (100%) to maintain identical level of hearing\textsuperscript{122}.

The conclusion should be that Gamma Knife radiosurgery allows hearing preservation in patients with smaller vestibular schwannoma with good initial hearing. The consequence is the recommendation of an early radiosurgical treatment before the hearing has deteriorated.

The topographical factors associated with hearing function after GKRS was analysed in 102 consecutive patients with vestibular schwannomas (mean prescription dose 11.9 Gy). Within the mean follow-up of 55 months, the crude tumor growth control was 92%. Hearing was preserved in 57% of patients with initially serviceable hearing. It was suggested that presence of intrameatal tumor extension up to the fundus may be associated with somewhat greater risk of functional deterioration after irradiation\textsuperscript{122}.

This potential relation of tumor location to functional status was further analysed in 176 patients with unilateral acoustic neuromas treated in Pittsburgh, where the potential prerequisites for hearing deterioration according to MR prior to Gamma Knife stereotactic radiosurgery were tested. It was confirmed that tumor volume in the internal auditory canal significantly correlated with GRC hearing. Hearing worsened as the total tumor volume increased. However, even small tumors frequently presented with major hearing impairment, but the concept that hearing would be worse when the lateral tumor margin reached the cochlea was not supported\textsuperscript{124}.

Even with the most conformal SRS devices available, and specific “cochlea shielding” strategies, there is still very little that can be done to limit dose to the cochlea when the tumor extends to the fundus of the internal auditory canal\textsuperscript{21}. Jeffrey Jacob asked the provocative question if – by reporting cochlea dose as it relates to hearing outcome – we may only be reporting what we can measure rather than what is truly impacting outcome\textsuperscript{21}.
Preserved hearing with regard to Pre-SRS SDS; from Jeffrey Jacob121

Preserved hearing with regard to mean cochlear volume dose <5Gy vs ≥5Gy. from Jeffrey Jacob121

Hypofractionation

A potential treatment option for larger vestibular schwannomas is fractionated or hypofractionated stereotactic radiosurgery which was analysed in a small study of 79 patients with 49 patients with acoustic neuromas, where 49 received fractionated stereotactic radiosurgery (average: 3 fractions, mean dose 18 Gy, mean volume 2.4 cc) and 30 patients who received single fraction radiosurgery (mean dose 12.5 Gy, mean volume 1.8cc, median f/u for Group A was 39 months and for Group B 18 months). In this small series with short follow-up, fractionated radiosurgery achieved tumor control in 92%. A total of 65% had no change in useful hearing. The results were similar for single fraction radiosurgery with tumor control rates of 90% and maintained useful hearing in 67%. The results were interpreted that a multi-fractionated stereotactic treatment regimen had no benefits in the treatment of an acoustic neuroma125, but the follow-up in this study was too short to allow conclusions with regard to tumor control.
Radiosurgery has opened a new paradigm of functional integrity in the management of vestibular schwannoma with the consequence of classical neurosurgical results being questioned as to their inherent perioperative morbidity. The result is the comparatively new approach of a safe and partial tumor removal that allows the preservation of functions combined with radiosurgery of the remaining tumor to prevent further growth. A series from Lausanne was presented that had prospectively analyzed this combined approach, i.e., the planned subtotal resection followed by Gamma Knife radiosurgery on the postoperative residual tumor for the management of 16 large skull-base lesions, including vestibular schwannomas (mean presurgical tumor volume: 16 cc). Postoperative status showed no facial nerve deficits. Five patients with useful pre-operative hearing underwent surgery with the aim to preserve cochlear nerve function; of these patients, 4 remained in GR class 1 and one lost hearing126.

Yoshiyasu Iwai evaluated the functional preservation of hearing in planned partial surgical resection followed by GKRS in 40 patients of large unilateral vestibular schwannomas with intentional partial tumor removal for functional preservation (mean maximum tumor diameter: 35.1 mm, range 25-52 mm). GKRS was performed 3-6 months after surgical resection. (median tumor volume at GKS was 3.3 cm³ and prescription dose 12 Gy, mean follow-up 63 months). The combined approach allowed the functional preservation of the facial nerve in 95% at the final follow-up. Among the patients with some hearing preservation before surgery, 73% maintained same hearing levels (<20 dB deterioration) after surgical resections. At the last follow-up, 45% had maintained the same hearing levels as before GKRS127.
Neurofibromatosis Type 2

In patients with neurofibromatosis type 2 (NF2) who were studied with a very long mean observation period of 112 months at the Beijing Neurosurgical Institute, the overall tumor control rate was 88.6% and hearing preservation rate was 37.2% and the rate of transient or permanent facial paralysis was unusually high with 10.3%. In another study from the Shanghai Gamma Hospital with 113 patients treated with GKRS for vestibular schwannomas associated with NF2 (median tumor volume 3.2 cc, mean follow-up time 35 months), the radiographic control rate was 82% at 2 years and 67% at 5 years and the hearing preservation rate was 44% at 5 years. Even here, there was an unusually high rate of 31% of new partial facial weakness. The authors reported that 34/35 of these cases were unrelated to radiation toxicity—a statement that would require a more detailed analysis. It should be noted that a previously published long term series with 122 tumours in 92 patients, (906 patient-years of follow-up) described a 5% risk for facial palsy. Furthermore, it was estimated that 8 years after radiosurgery for NF2 VS, 50% will be well controlled and 20% of patients will have required further treatment.

Malignant Transformation

The significance of radiation in the induction of malignancy in vestibular schwannoma after radiosurgery is still not quite clear, although a number of case reports have been published. Michael Torrens described a new case of verified induction of malignant peripheral nerve sheath tumor (MPNST) in a vestibular schwannoma. This patient is the 26th reported case of verified malignant transformation after radiation. Eight of the cases were patients with NF2. Additional 20 cases of malignant transformation have been reported in patients who had not been irradiated before. The author drew the conclusion that despite recent reports of malignant transformation in vestibular schwannoma after radiation, only in NF2 cases the incidence of malignancies appears to be notable in relation to the numbers treated. Radiation treatment including SRS can potentially induce malignancy in vestibular schwannoma, but the risk appears to be small in the region of 0.01% – 0.02%. This has to be compared with a realistic mortality rate after craniotomy of at least 1%.
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.

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. However, not all series could establish a relation between dose and outcome. 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 Adenoma

In cases of smaller non-secreting pituitary adenoma, Gamma Knife radiosurgery appears to be a safe option providing consistent and reproducible tumour control with very low risk for immediate side effects. The risk of developing pituitary endocrinological deficits is estimated at 32% 5 years after radiosurgery. In general, radiosurgery is applied for remnant tumors after a surgical resection. With regard to the predictable outcome and low level of side effects however, Gamma Knife radiosurgery can be considered even as a first line treatment in smaller non-secreting pituitary adenoma.

Under the auspices of the North American Gamma Knife Consortium (NAGKC), nine Gamma Knife centers retrospectively combined their outcome data in a very large series of 512 patients with non-functional pituitary adenomas (median prescription dose 16 Gy, median follow-up 36 months). Prior resection had been performed in 479 patients and prior fractionated external beam radiotherapy applied in 34 patients. Actuarial tumor control was 98%, 95% and 91% at 3, 5 and 8 years post-radiosurgery.

New or worsened hypopituitarism after radiosurgery was noted in 21.1% of patients, with thyroid and cortisol deficiencies reported as the most common post-radiosurgery endocrinopathies. New or progressive cranial nerve deficits were noted in 9.3% of patients; 6.6% had worsening or new onset optic nerve dysfunction. No patient died as a result of tumor progression. A large series from the Ospedale San Raffaele in Milano was presented with 238 patients with a diagnosis of non-functioning pituitary adenoma (NFPA) and secreting pituitary adenoma (SPA) in 249 patients. All patients had been treated surgically and were treated with GKRS for residual pituitary tumor (medial marginal dose 15.4 Gy for NFPA and 23.1 Gy for SPA, the dose to the optic pathways <10 Gy, mean FU after GKRS 68.75 months). Only 5.1% showed recurrences and of those, 72% were outside the radiation field. Current doses were found to be adequate for growth control, since only 1.4% developed in-field recurrences following GKRS.
Secreting Pituitary Adenomas

When compared with a second transsphenoidal adenomectomy, a higher recurrence-free interval was shown after Gamma Knife treatment of patients with relapse of Cushing’s disease (n=52), who had randomly undergone either second surgery or GKRS as the next therapeutic approach. In a series of 91 patients with functional pituitary microadenomas, the hormone level was normalized in 42.8% patients, partly recovered in 25.3% and showed no change 16.5%, and increased 15.4%. For 56 patients with prolactin secreting microadenomas, the serum prolactin decreased in 41.1% patients. Similarly others reported a biochemical remission occurred in 45.3% (58/128) at mean prescription doses of 26Gy, with highest success rate being among ACTH secreting adenoma patients. Hormonal normalization occurred at a mean of 20.4 months (6-84 months), the earliest among prolactinoma patients. In a series with 128 pituitary microprolactinoma treated with GKRS serum prolactin normalised or decreased in 87% (prescription dose 23 Gy).

Threshold Doses for Radiation-Induced Optic Neuropathy

The radiosurgical and radiotherapeutical dose thresholds for visual complications have been defined based on relatively small series using older technology. Data that further define the dose thresholds for the optic nerves and define the boundaries of single session radiosurgery are highly relevant. The following study aimed at determining the dose-volume tolerance of the optic nerves and chiasm in 116 patients with pituitary adenomas treated with GKRS without previous radiation. The median maximum point dose to the anterior visual pathways was 9.2 Gy (2.4-14.5), 64% of measured sides received > 8 Gy, 35% of sides received > 10 Gy and 12% of sides received > 12 Gy. While formal ophthalmological testing after SRS was not available for 19%, it appeared as noteworthy that no tested patient had a documented decline in their visual function after SRS. The 95% confidence interval of developing a radiation-induced optic neuropathy at the 8-Gy, 10-Gy, and 12-Gy volumes in this series were 0-3.0%, 0-5.4%, and 0-14.8%, respectively. The conclusion of the authors was, that the anterior visual pathways in patients without prior radiation treatments can safely receive radiation doses up to 12 Gy with a low risk of radiation-induced optic neuropathy. These data will have to be confirmed in larger studies before they can be applied safely in clinical practice.
Other Benign Tumors

Central Neurocytoma
A retrospective analysis of 36 patients with central neurocytoma who had been treated with GKRS in 12 institutions in Japan was presented with cumulative local tumor control rates of 94% and 86% at 5 and 10 years, respectively. Three patients developed distant dissemination (mean tumor volume 6.4 ml, mean prescription dose 15 Gy, mean follow-up 57.5 months)132.

Facial Schwannoma
Ten cases of facial schwannomas were reported: marginal dose of 12 Gy, mean clinical and radiological follow-up 44.6 months. Overall tumor control rate was 100%. Postoperative facial palsy was seen in 20% of patients (transient: 10%). Hearing deterioration was seen in 20%133.

Trigeminal Schwannoma
In one of the largest series of trigeminal schwannomas in 53 patients treated by GKRS, the actuarial 5- and 10-year progression-free survival rates were 90% and 82%, respectively (median tumor volume 6.0 cm³, median marginal doses 14 Gy, median follow-up period 98 months). The conclusion was that GKRS can be an acceptable alternative to surgical resection in patients with trigeminal schwannomas. However, large tumors compressing the brainstem with deviation of the fourth ventricle should be removed surgically134.

Glomus Tumors
A retrospective study analysed the outcome in 44 patients with glomus tumors; open surgery had preceded radiosurgery in 46%, embolization in 17% and fractionated radiotherapy in 4% (mean tumor volume 3.6 cm³, range: 0.2-24.3 cm³, median prescription dose 20 Gy, range: 10-30 Gy). With a median follow-up period of 110 months, tumor size decreased in 77%, showed no change in 20% and increased in 2%. A prescription dose of > 15 Gy is recommended (data from slides)135.

Craniopharyngioma
In patients with craniopharyngioma treated with GKRS, tumor progression free survival rate was 72% after 5 years and 38% after 10 years follow-up (n=113, median tumor volume 5.6cc, median prescription dose 12 Gy, follow-up 41 months). Although 9 patients died during follow-up, mortality was related to tumor progression in only 4 patients142. Tumor control rate was 79.2% in another study of craniopharyngioma (n=24, mean volume 2.5 ml, mean prescription dose 11.96 Gy, mean follow-up period 64.1 months). Actuarial survival was 96% and 80% after 5 and 8 years, respectively, however, PFS was 79.5% and 53% after 5 and 8 years. Two patients died of hypothalamic invasion of tumor at 14 and 8.5 years after the diagnosis143.
A prescription dose of > 15 Gy is recommended for the treatment of glomus tumors (data from slides) from Roman Liscak.

Long-term follow-up after Gamma Knife treatment of a glomus tumor; from Roman Liscak.
After standard fractionated radiotherapy, 77%-90% patients relapse within 2 cm of the original glioblastoma within 20-40 weeks. 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. Stereotactic radiosurgery has been used as the treatment for glioblastoma as up-front treatment or for recurrent tumors. When compared to other technologies, Leksell Gamma Knife is superior in terms of radiation dose gradients and accuracy.

In the current literature, salvage stereotactic radiosurgery was used in 16 studies and 643 patients in the treatment of glioblastoma recurrences. Overall survival was reported in 11 studies (422 patients) as ranging between 16.7-33.2 months.

In 9 out of these 11 studies comprising 88% of published patients (370/422 patients) 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. There were 14/16 studies comprising 590 patients that reported the survival specifically after radiosurgical treatment for the glioblastoma recurrence ranging between 6.5 and 30 months. In 10 out of those 14 studies representing 82% of published patients who had been treated with salvage radiosurgery (486/590), the median survival was 10-30 months after 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 minimally invasive treatment strategy for glioblastoma recurrences in a situation when only very few alternative options exist.

Christopher Duma described that glioblastoma multiforme cells migrate along predictable white matter pathways; his hypothesis is that this spread may be blunted by high-dose, single-fraction radiation. He claims that it has been shown that glioblastoma cells will undergo apoptosis if rendered unable to migrate. The hypothesis is that targeting white matter pathways, adjacent to the original enhancing tumor site (“Leading Edge”© GKRS) should improve survival for patients with glioblastoma. A total of 109 patients with newly diagnosed glioblastoma were treated with GK radiosurgery to the “Leading Edge”© of tumor cell migration as defined as the region outside the enhancing, tumor nidus, defined by FLAIR MRI and/or MR spectroscopy. Subjectivity in choosing the “Leading Edge” is the main limitation of the technique. A median volume of 33.5 cm³ of tissue was targeted using a median prescription dose of 8 Gy. The overall median survival from time of diagnosis was 23 months and 43% were still alive at 2 years, 19% at 3 years, 12% at 5 years. Admission and mannitol for radiation induced edema was necessary in 9% and permanent complications were seen in 6%©. In this context it is interesting to see an in vitro study that showed that low-dose gamma knife radiation of 6–8Gy could even increase the invasive ability of glioma cell lines (U87 and U251)©.
Patients with recurrent glioblastoma were retreated with low-dose GKRS (median prescription dose 10Gy) after failed multimodal treatment including surgical resection, chemotherapy and fractionated external beam radiation therapy. Average time from first surgery to GKRS was 17 months. \(n=42\), median target volume 5.1ccm) Median overall survival was 25.6 months from time of diagnosis, 19% showed radiation induced edema, 2.4% necrosis and 2.4% cysts. Median survival after first GKRS was 9.6 months\(^{146}\). Higher doses were applied in 18 patients with recurrent GBM treated with GKRS. The treatment target consisted in the contrast-enhancing lesion on MRI imaging (median treatment volume 7.3 cc, median marginal dose 18 Gy). Similar to the previous study, median overall survival time was 12 months following GKRS treatment. The local recurrence rate was 50% at 3 months, and 76% at 6 months. Only one patient developed significant toxicity with surgically resected radiation necrosis following GKRS\(^{147}\). A higher rate of side effects was reported in another study of 55 patients with high grade glioma (WHO III and WHO IV) who had been treated with GKRS for local recurrences at higher doses (median tumor volume 5.2 cc, prescription dose: 20 Gy). In 40%, there were secondarily increasing contrast enhancing lesions that were considered as adverse radiation effects. Median survival in WHO III patients after GKRS of the recurrences was 24.2 months and median survival in WHO IV was 11.3 months\(^{148}\). A similar rather positive survival time of 20.2 months since initial diagnosis was shown in another study with 63 patients with recurrent GBM: Median survival following GKRS salvage therapy was 9.9 months for all patients with KPS being a significant predictor of survival.

The outcome appears to be promising when compared to an expected survival of 11.2 months for patients in Class IV after conventional therapy\(^{149}\). A similar survival was reported in 33 patients with WHO grade IV gliomas who were treated with GKRS, the average post-GK and overall survival was 15.8 months and 40.1 months respectively. In WHO grade III gliomas, the average post-GK and overall survival was 34.9 months and 136.4 months respectively. Even here, 67% patients showed edema after GKRS, with 14/33 requiring dexamethasone\(^{150}\).

The conclusion is that Gamma Knife radiosurgery may be an additional option in the treatment of recurrent malignant glioma and glioblastoma with promising overall survival in a situation that otherwise is considered untreatable. Further information is required to define the ideal imaging modality, the target and doses, since the low-dose studies appear to provide a similar treatment effect at a lower risk for radiation induced side effects.
Low-Grade Gliomas

Pilocytic astrocytoma (WHO grade I) are generally surgically resected. However, due to the generally central and often eloquent tumor location, a significant number of patients are considered inoperable or are left with postoperative tumor remnants. Gamma Knife radiosurgery is a low invasive treatment option for this relatively rare indication in an otherwise complicated clinical situation. The long-term outcome of 30 patients with pilocytic astrocytoma treated with GKRS (median prescription dose 10 Gy) and median clinical and radiological follow-up of 12.2 years and 10.9 years, respectively, showed a local control of the solid tumor component in 90% and a 93% survival at the end of the follow-up period. A virtually identical tumor control rate of 93.5% was achieved in 46 patients with pilocytic astrocytomas after GKRS at a mean follow-up of 48 months (mean tumor volume 5.5 cc, mean prescription dose 13.1 Gy). In 11/18 patients, where cysts were present at GKRS, the cysts increased and 4 out of 45 patients developed new cysts. Seizures improved in 6/15 patients. Associated clinical deterioration occurred in 15.6% which was temporary in all but one case (cited according to slide).

Stereotactic fractionated radiotherapy was used in 102 patients with pilocytic astrocytomas (mean dose 54.8 Gy), while 54 patients underwent single session Gamma Knife treatment (mean dose 17 Gy) with a median follow-up of 34.7 months. Tumor control was achieved in 79.8%. In the vast majority of patients (23/28), where tumor volume enlarged during the follow-up, the increasing size was the result of enlargement of cystic components. Similarly, 19 patients were treated in 5 fractions (1 fraction per day), and 5 patients received single fraction treatment for pilocytic astrocytoma and were followed for a minimum of 10 years at the Na Homolce Hospital in Prague. Patients slept with the stereotactic frame attached (maximum 4 nights). The median target volume was 2.7 cc (range 0.2-25 cc) and the median minimal total target dose (for all fractions) was 25 Gy. Complete regression occurred in 40% and partial regression in 40%. Overall detected surviving fraction after 10 years was 96%. Later progression of cysts was seen in 16% (cited from slides).

In conclusion, Gamma Knife radiosurgery allows the long-term tumor control in pilocytic astrocytoma with minimal morbidity. Cyst development is rather frequently seen during follow-up and may require separate treatment.
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 pain is located in the areas supplied by the trigeminal nerve in the face.

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 on just one side of the face. Often the pain responds to medication, but sometimes the dose has to be increased and unpleasant side effects can occur. An invasive and generally surgical procedure is recommended for patients who continue to experience severe pain or side effects from medications. Gamma Knife radiosurgery achieves similar results without open surgery and without general anesthesia. Gamma Knife radiosurgery is the most recent and least invasive neurosurgical treatment for trigeminal neuralgia. Through focal irradiation of the trigeminal nerve close to the brain stem the facial pain can be treated successfully without impairment of other nerve functions.

Significant pain relief can be achieved in 73% of patients at 1 year, in 65% at 2 years, and in 41% at 5 years, respectively. Most published series show a similar outcome with significant pain relief between 73 and 86% of patients after the Gamma Knife intervention. After radiosurgery, about 10% of patients may be mildly affected by facial paraesthesias. In a presented retrospective study 130 patients with essential Trigeminal Neuralgia were followed up at least 5 years after GKRS and 66% were completely pain free at the last follow-up up (90 Gy at maximum dose, one shot of 4 mm collimator). Patients with previous surgical microvascular decompression (MVD) appear to have a lower chance of being pain free after GKRS compared to patients without previous MVD history: Retrogasserian GKRS after previous MVD (n=45) showed an initial pain free rate of 77.8%, and the probability of remaining pain free at 3, 5 and 10 years was 66.5%, 59.1% and 44.3%, respectively.
The optimal target position in trigeminal neuralgia has been discussed with regards to pain relief and side effects, and it has been claimed that facial hypoesthesia after GKRS could be avoided through a more anterior placement of the isocenter creating a longer distance towards the root entry zone at the brain stem. This was studied in 106 patients where the dorsal root entry zone was targeted with a maximum dose of 90 Gy. It appeared that the pain relief and pain recurrence was not influenced by differences in distance between the target and brain stem, while radiation-induced facial hypoesthesia appeared to result from a more proximal target.

Volume differences between affected and unaffected trigeminal nerves have been described, and the volume of the trigeminal nerve on the affected side was shown to be significantly smaller than the volume of the unaffected side, but the evaluation of nerve volumes along their course through the pontocerebellar cistern (n=55) did not support the hypothesis that volume changes are a predictive factor for successful treatment by GKRS. Another study documented no statistically significant differences in cross sectional areas or nerve volumes between affected and unaffected trigeminal nerves and no difference in cross sectional area at the root entry-zone, midpoint, nerve entry point to Meckel’s cave, or nerve volume between normal and affected nerves (n=68).
Radiobiological aspects suggest an influence of the radiation dose rate on the outcome after radiosurgery. Hence, the clinical impact of the radiation dose rate was tested in 497 patients with classical trigeminal neuralgia who had been treated with GKRS at a median maximum dose of 85 Gy. Patients were divided into 2 groups: a low dose rate group (LDR, 0.891-2.513 Gy/minute; n=210) and a high dose rate group (HDR, 2.514- 4.099 Gy/minute; n= 208). A total of 50.5% were pain free in the LDR group and 49.5% in the HDR group, respectively (p=0.69) and 20.1% developed new or increased facial sensory dysfunction and 33.8% had a recurrence. However, within the tested range between 0.891 and 4.099 Gy/minute, the variation in dose rate did not affect the rate of freedom of pain, the onset hypoaesthesia or the probability of recurrence after GKRS for trigeminal neuralgia.

In cases of recurrent pain, GKRS can be repeated. It can be estimated that 83% of patients will experience pain relief from a second GK procedure with side effects in 10.5% including facial numbness, corneal dryness and difficulty swallowing; however, only 5% of these patients found these effects to be bothersome (n=38). The conclusion was that repeat GKRS proved to be effective with an acceptable risk of side effects.

In patients with multiple sclerosis-related trigeminal neuralgia the outcome of GKRS has been reported to be less favorable which is in line with the results of all other treatment modalities in this condition. While 90.7% (39/43) of these patients were initially pain free within a median of 30 days, 61.5% experienced a pain recurrence after a median delay of 16 months and hence their probability of remaining pain free at 1, 3 and 5 years was 71.8%, 43.1% and 38.3%, respectively. The high rate for the recurrence of the trigeminal pain is specific to this clinical entity.

Even glossopharyngeal neuralgia has been treated with GKRS. In a small study all patients (n=5) improved between 3 and 6 months after treatment, three cases are without pain and without medication. No neurological deficit has been observed after the treatment. The glossopharyngeal nerve was targeted in the jugular foramen, a maximum dose of 90 Gy was administrated with a 4 mm collimator.
Gamma Knife Thalamotomy

Lesioning in functional neurosurgery has maintained an important role in the treatment of movement disorders and a variety of lesioning technologies are still available. A 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\textsuperscript{171}. The current options for lesioning procedures were reviewed by Takaomi Taira\textsuperscript{172}.

Gamma Knife provides a non-invasive option for functional lesions in movement disorders and even in selected cases of psychosurgery. The neurological outcome after unilateral VIM Gamma Knife thalamotomy for Parkinsonian's or essential tremor was evaluated in 95 treated patients showing that 75% of patients clinically responded to thalamotomy. The mean clinical improvement score was 61.5%. One very large lesion was described but excluded from the analysis. The conclusion was that VIM Gammaknife thalamotomy is a safe and effective option for intractable tremor\textsuperscript{173}. Virtually identical results were reported in a series from Warsaw, after Gamma Knife thalamotomy for the treatment of Parkinsonian and essential tremor, where 76% of patients became tremor free or nearly tremor free (n=48, median radiation dose 130 Gy). Two types of tissue reaction were observed on follow-up MR imaging: an oval necrotic lesion up to 5-7 mm without surrounding edema and a complex irregular shaped necrosis with thalamus/midbrain edema. In the group of the last 18 patients, DTI was utilized analysis to visualize internal capsule fibers that are in the vicinity of VIM nucleus\textsuperscript{174}. Another series with 20 patients who underwent Gamma Knife VIM thalamotomy (130 Gy, single 4 mm collimator) showed significant tremor relief in 85%, with complete relief in 50%\textsuperscript{175}.

Patients with essential tremor either only or predominantly affecting axial structures, including the head and neck, voice or lower jaw, respond to staged bilateral Gamma Knife VIM thalamotomy (n=68; maximum dose 140 Gy, mean follow-up is 65 months). The results are comparable to those seen after bilateral Deep Brain Stimulation. Head and neck tremor improved in the applied tremor scale from a mean of 3.1 +/- 1.2 preoperatively to 2.2 +/- 1.1 after unilateral Gamma Knife thalamotomy and to 1.1 +/- 0.7 after bilateral thalamotomy. Similar, statistically significant improvements were seen in both voice and lower jaw tremor. Two patients experienced complications including speech, balance and gait problem of the total of 136 procedures\textsuperscript{176}.

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\centering
\includegraphics[width=\textwidth]{image.png}
\caption{The functional VIM target in 7T and 3T MRI. From Constantin Tuleasca\textsuperscript{169}}
\end{figure}
Imaging and Thalamotomy

High-resolution susceptibility weighted images at 7Tesla MRI provided a superior resolution and an improved image contrast within the central gray matter and allowed visualization of thalamic subparts to improve anatomic imaging for Gamma Knife radiosurgery of VIM. The 7T images could be imported into the Leksell Gamma Plan® software and co-registered with stereotactic images\textsuperscript{169}. On the other hand it was shown that susceptibility artifacts in the interfacing areas of paranasal sinus and skull base can impair the acquisition of detailed images in the 7.0T\textsuperscript{5}.

As an alternative, a novel approach using 3-T multiband DTI appears to delineate most internal nuclei of the thalamus based on differences in track density and/or diffusion anisotropy at 500-micron resolution. The results appear significantly improved compared to previous diffusion tensor imaging parcellations of the thalamus\textsuperscript{170}.
Imaging Accuracy

The delineation of target is a manual process, influenced by both experience and image quality. Significant differences and variability in target identification were demonstrated between radiosurgical centers emphasizing the importance of understanding target definition in stereotactic radiosurgery\textsuperscript{166}.

MRI is the primary imaging modality used for Gamma Knife radiosurgery, yet inherent distortions with this imaging modality are well known. Using two different target phantoms, image distortion at different points in the clinical target area were measured for multiple protocols on 57 MR scanners at 45 Gamma Knife sites. The mean and maximum errors for 57 tested MR scanners were 0.76 mm (range 0.40 to 1.58 mm) and 1.27 mm (range 0.78 to 3.78 mm) respectively.

Mean errors measured with a phantom were on average 1.6 times larger than the mean fiducial errors quoted by LGP, while maximum errors were about the same. The mean and maximum errors for all CT scanners investigated (n=30) were 0.46 mm (range 0.23 to 0.98 mm) and 0.81 mm (range 0.45 to 1.96 mm) respectively\textsuperscript{167}.

It is generally accepted that targets that are located above the MR fiducial box can be treated. A quantitative evaluation showed that targets up to 36 mm over the fiducial box are safely treated, since the effect of not having fiducial is not expected to alter the MR information by more than ±0.1 mm\textsuperscript{168}.
Stereotactic hypofractionation using the Gamma Knife was applied in pilocytic astrocytoma\textsuperscript{114}, vestibular schwannomas\textsuperscript{125}, large meningiomas\textsuperscript{111}, perioptic meningioma\textsuperscript{112} and for large brain metastases (>10cc in volume\textsuperscript{22})\textsuperscript{177}. The results are discussed in the respective sections.

A technical alternative to the Extend frame was presented that allows fractionated GKRS using a relocatable frame: four plastic fiducial screws are mounted in the outer surface of the skull prior to MRI imaging. For MRI, fiducial markers are attached on the fiducial screws, producing a stereotactic image without merging or co-registration. The fiducial screws function both as fiducial markers and fixation devices for a stereotactic frame. After MRI, a relocatable Leksell G frame is attached to the fiducial screws. A feasibility study demonstrated stability and reproducibility\textsuperscript{177}.

Jonathan Knisely reviewed the pros and cons for fractionated stereotactic radiosurgery and came to the conclusion that there is still no strong evidence base upon which to recommend fractionated radiosurgery, since there are no class I data comparing single-fraction radiosurgery to fractionated radiosurgery\textsuperscript{178}. 
Orbital Lesions

The effect of GKRS in 31 children with orbital lesions was reported (median age 6 years; mean prescription dose 15.9Gy, median follow-up: 32 months). No further tumor enlargement was observed after GKRS. 25.8% had an improvement in their symptoms, and remained stable in 58%, and deteriorated in 16.1%. The most common complication was reversible conjunctival edema usually within 3 months. No other serious acute adverse effects were observed\(^{179}\).

Ophthalmologic Indications: Stenopeic Eye Fixation

Due to eye ball movement, radiosurgery of intra orbital lesions typically requires the surgical fixation of the eye during image acquisition and dose delivery. Instead of this comparatively invasive approach, a simple and non invasive fixation solution was presented using a plate with a pinhole for each eye. The plate is fixed to the anterior posts of the frame. The eye ball is naturally fixed when the patient is looking through the pinhole of the side of the lesion during both MRI and dose delivery. So far 10 patients with orbital lesions have been treated relying on this eye fixation system and the authors stated “a sufficient residual visual acuity”\(^{180}\).

Glaucoma

A retrospective series after GKRS in the treatment of secondary glaucoma compared the 2-year results with the 7-year results in 57 patients. The authors had used four shots using 8 mm collimators to irradiate the ciliary body (prescription dose 20 Gy for blind eyes and prescription dose 15Gy for partially preserved vision). The average follow-up was 82 months. The conclusion was that GKRS can effectively achieve reduction of pain, intraocular pressure and extensive pharmacotherapy in secondary glaucoma\(^{181}\).
Novel Approaches

Gamma Knife Hypophysectomy for Cancer Pain

In an interesting novel approach 21 patients with cancer pain were treated with Gamma Knife radiosurgery lesioning of the anterior lobe of the pituitary gland with 140-180Gy maximum dose using one shot of the 8 mm collimator. A total of 90.5% of the patients experienced significant pain reduction without significant complication except for endocrinological impairment.156

Modern Genetic Approaches to Glioma

Robert Darnell, New York, NY182

Robert Darnell’s lab has discovered that neurons have unique systems for regulating gene expression, but not at the level of DNA transcription. Rather, these systems regulate RNA metabolism via neuron-specific RNA binding proteins. Many different RNA variants, and consequently protein variants, can be generated by this system. To understand this regulation in the brain, Robert Darnell’s lab has developed a high throughput genomic method termed HITS-CLIP to precisely map relevant protein-RNA interaction sites with single resolution. Relevant systems that are undergoing current analysis include RNA control and dysregulation in brain tumors, in chronically stressed brain in Alzheimer’s disease, and in ischemic brain. Robert Darnell discussed these studies along with their relevance and applicability to various clinical scenarios and with a focus on genetic approaches to glioma.182

A Stem-Cell Based Surgical Transplantation Therapy for Parkinson’s Disease

Ole Isacson, Boston, MA183

The experimental field of restorative neurology continues to advance with implantation of cells or transfer of genes to treat patients with neurological diseases. Both strategies have demonstrated their capacity for structural and molecular modification in the adult brain. However, both approaches have yet to successfully address the complexities of actual clinical applicability. New non-pharmacological treatment strategies involve cell and synaptic renewal or cell replacement in the living brain to restore the function of neuronal systems, including the dopaminergic (DA) system in Parkinson’s disease. The experimental cell transplantation to patients with Parkinson’s disease (PD) utilizes dissected pieces of fetal midbrain tissue as donor cells. Stem cell and progenitor cell biology provide new opportunities for selection and development of large batches of specific therapeutic cells. This may allow for cell composition analysis and dosing in order to create a benefit for individual patients. The biotechnology used for cell and gene therapy for treatment of neurological disease could eventually become as advanced as today’s pharmaceutical drug-related design processes. Current gene therapy phase 1 safety trials for PD include the delivery of a growth factor (neurturin) and a transmitter enzyme (glutamic acid decarboxylase and aromatic acid decarboxylase).
Although recent laboratory work has focused on using stem cells as a starting point for exogenous or endogenous derivation of the optimal DA cells for repair, DA cell therapy using dissected fetal DA tissue containing neurons has already been explored in PD patients. Human fetal dopamine ventral mesencephalic neurons have been shown to be functional in clinical trials in PD patients.

Many new insights from cell biological and molecular studies provide opportunities to selectively express or suppress factors relevant to neuroprotection involved in Parkinson’s disease. Future gene and cell therapies are likely to coexist with classic pharmacological therapies because their use can be tailored to individual patients’ underlying condition. Open-label trials consistently demonstrated that functional motor deficits associated with Parkinson’s disease can be reduced after application of this new technology, but so far double-blind trials failed to show evidence of significant benefit in comparison with placebo. The field was reviewed by Ole Isacson²⁸³.
Focused Ultrasound: The New Frontier?
Jessica Foley: Focused Ultrasound Foundation, Charlottesville, VA USA

Circa 1950 Lars Leksell invented focused ultrasound as a less invasive alternative to open surgery for the treatment of movement disorders. However, after treating a number of patients, he abandoned this technology because it required a craniotomy and because there was no imaging technology to enable effective guidance, monitoring, and control of the treatment. At that time, there was no option to focus beams of ultrasound on a target in the brain through the intact skull. Currently, focused ultrasound is experiencing a renaissance. As a result of advances in ultrasound transducer design, high-speed computing technologies and MR imaging, focused ultrasound now has the potential to treat a variety of intracranial disorders noninvasively. Indications at various stages of research and development currently include movement disorders, brain tumors, epilepsy, neuropathic pain, OCD, thromboembolic and hemorrhagic stroke. Near-term studies on blood brain barrier opening and neuromodulation are also planned. The new developments were reviewed by Jessica Foley.

Neuro-Immunology and Therapeutic Radiation
Kevin Tracey, Manhasset, NY

The autonomic nervous system maintains homeostasis through its sympathetic and parasympathetic divisions. During inflammation, cells of the immune system release cytokines and other mediators that cause fever, hypotension, and tissue injury. Although the effect of cytokines on the nervous system has been known for decades, only recently has it become evident that the autonomic nervous system, in turn, regulates cytokine production through neural pathways. Neural circuits regulate cytokine production to prevent potentially damaging inflammation.

It has previously been shown that efferent vagus nerve signals inhibit TNF-α production in spleen by a mechanism requiring acetylcholine signaling through the α7 nicotinic acetylcholine receptor expressed on cytokine-producing macrophages. This mechanism has been termed “the cholinergic anti-inflammatory pathway”. Nerve fibers in spleen lack the enzymatic machinery necessary for acetylcholine production, but an acetylcholine-producing, memory phenotype T cell population in mice has been identified that is integral to the inflammatory reflex. These acetylcholine-producing T cells are required for inhibition of cytokine production by vagus nerve stimulation.

Thus, action potentials originating in the vagus nerve regulate T cells, which in turn produce the neurotransmitter, acetylcholine, required to control innate immune responses. This mechanism can conceptually be modified by vagus nerve stimulation, which so far has been used to treat patients with rheumatoid arthritis.
Neural circuits can regulate cytokine production. From Kevin Tracey\textsuperscript{185}

During endotoxemia, vagus nerve stimulation specifically attenuates TNF-\(\alpha\) production by spleen macrophages in the red pulp and the marginal zone. The cholinergic anti-inflammatory pathway regulates TNF-\(\alpha\) (alpha) production in discrete macrophage populations via two serially connected neurons: one preganglionic, originating in the dorsal motor nucleus of the vagus nerve, and the second postganglionic, originating in the celiac-superior mesenteric plexus, and projecting in the splenic nerve. The modulation of this circuit could potentially attenuate the outcome in patients with septic shock\textsuperscript{185}.\textsuperscript{185}
The collateral dose to normal tissues during treatment continues to be an area of interest, being a hallmark of radiosurgery treatment. With a trend towards an increased number of metastases treated per patient, some Gamma Knife users are insecure about the dose to the normal brain being within acceptable limits.

Ian Paddick spoke on brain doses from the treatment of multiple metastases with the Gamma Knife. He compared dose volume histograms from a GK plan for 28 metastases with those from WBRT (30Gy in 10 fractions). The Gamma Knife plan had around an order of magnitude less dose to the whole head, i.e., about the level of just one fraction of WBRT. This low dose corroborates a safety that even allows multiple treatment sessions. In an extreme example, of 114 metastases managed with Gamma Knife over 5 sessions in 15 months, there was again a very low whole head dose which was approximately equivalent to a single fraction of WBRT, once sub-lethal repair had taken place in between each treatment session.

Lijun Ma backed this up with his latest publication; ‘Variations in dose interplay across radiosurgical apparatus in treating brain metastasis’. Ma’s goal was to benchmark Truebeam Flattening Filter Free (FFF) linac technology with results already published for Gamma Knife, Cyberknife and Novalis. Gamma Knife was shown to be overall the most conformal of all the radiosurgery platforms and also gave up to 74% lower dose to normal brain tissue. Even when up to three non-coplanar arcs were used with the Truebeam platform, normal brain doses were still far higher than those from the Gamma Knife.

Brain Doses from the Treatment of Multiple Metastases
Technological Developments

The next Gamma Knife model is always an intriguing subject. A number of excellent presentations were made by physicists from Elekta’s R&D department, covering topics related to the development of the next generation Leksell Gamma Knife. Håkan Nordström talked about cone beam CT (CBCT) image quality, and the difficulties of the high scatter component of cone beam CT. Jonas Johansson spoke about the potential increases in skin dose from mask fixation, which although significant, were still less than skin doses calculated by Leksell GammaPlan. The complexity of various issues related to the new Gamma Knife development were appreciated by the attendees. The detail of work carried out by the Elekta R&D team reassured us that every aspect of the development has been considered and thoroughly investigated.

Ian Paddick reminded us that even small changes to the radiosurgery platform can enhance the delivered treatment, in an historical review of how planning parameters (coverage, selectivity, conformity, gradient index and beam on time) have improved with each successive version of the Gamma Knife over the last 15 years. Interestingly, he also showed that recent enhancements to GammaPlan have contributed equally significant improvements to treatment plan quality, when compared with hardware developments.
Accuracy of Co-Registration

The co-registration tool in Leksell GammaPlan is loved by many, but still eyed with suspicion by some, as it is very difficult to quantify the accuracy of the process. Co-registration in GammaPlan is a simple but powerful tool that can be used in a number of ways. For example: co-registration of 3T MRI to stereotactic CT on the day of treatment gives a treating team the flexibility to obtain images of superior quality, using 16 or even 32 channel head coils, that are not compatible with the Leksell frame. The freedom to allow pre-planning in an unpressurised environment is also appreciated by some. However, there have been concerns regarding the accuracy of this process. Some novel presentations at the meeting have reassured sceptics of many concerns and suggested that co-registration to CT may be as accurate as a dedicated stereotactic MRI scan.

Francisco Li presented his work on co-registration accuracy in thalamotomy treatments, where the highest degree of accuracy is required. He found that co-registration of 3T MRI to CT gave lower errors than using 3T alone. Average deviation was less than 1mm. Using DTI to demonstrate the internal capsule helped further to define a consistent target. It may be that the additional confidence in the target outline gained by better 3T scanning outweighs the uncertainty in the co-registration process.

Håkan Nordström spoke about the co-registration algorithm, in connection with the next generation Leksell Gamma Knife project. During this project, an additional refinement step was added in the co-registration process, and a calculation of an estimated mean target registration error (TRE) was devised, giving an estimation of the accuracy of the process. For registration of MRI to CT, typical TRES were less than 0.1mm. This compelling work suggested that co-registration with CT can be very good indeed.

Target Outlining

Is target outlining a source of inaccuracy in our treatments? Helena Sandström updated us on her excellent work, looking at the consistency in target outlining between 12 centers. Each center was asked to outline and plan 6 different targets. Even for a target as simple as a vestibular schwannoma, the common volume, agreed by all 12 centers, was just 50% of the aggregate volume drawn by at least one center. The inconsistency of target definition reminded us that this is still the least accurate process in the whole of radiosurgery.

Outside of the presentations, on a related matter, the Organ At Risk (OAR) Standardization Working Group, led by Caroline Chung, met and found common ground with the aim of producing a consensus document of contouring recommendations to improve consistency of outlining and hence the quality of prospective data collection to help establish radiosurgery-specific dose constraints.
Another major area of uncertainty is in the Biologically Effective Dose of treatment. This is proportional to the dose prescribed if the treatment is given at the same dose rate, but the dose rate is known to vary. Until recently, studies have only explored the effect of the reference dose rate of the machine with clinical effect. It is not surprising that this has shown no relationship. We often plan similar targets to the same dose, with resulting treatment times that vary by a greater range than the reference dose rate will ever do. Furthermore, each voxel ‘sees’ a dose rate that varies dramatically during treatment, depending on its proximity to every isocenter which makes up the overall treatment. John Hopewell showed the world’s first Biologically Effective Dose Volume Histograms (BEDVHs) of dosimetrically similar Gamma Knife treatment plans for vestibular schwannoma. This showed that the BED varied by up to 15% between plans prescribed to the same dose.

Viewing this in another way, while one plan had 100% coverage of a BED referenced to its prescription dose, the other plan had only 65% coverage of this same BED (3 isocenters vs 13 isocenters, Model B), despite both plans being prescribed to the same dose. Furthermore, due to the efficiency of treatment delivery, Perfexion treatments had about a further 15% increase in BED when compared with similar plans treated with the Model B.

One may ask why does a certain dose control a lesion in one patient, but not another? Granted, a range in inherent biological sensitivity is to be expected, but the answer to this question has never been quite clear.

A physicist is obsessed with ensuring consistent treatments. In terms of absolute dose, we have now nailed this down to just two or three percent, but new areas have opened up (target outlining, BED), showing us huge variations in the effective treatment we are giving. This gives a fantastic opportunity build on the work we have done and to address these variations, to give more consistent and better treatments to our patients.
NEW AND ONGOING STUDIES

Report of the North American Gamma Knife Consortium

Ajay Niranjan: University of Pittsburgh - Pittsburgh, PA USA

The North American Gamma Knife Consortium (NAGKC) was formed in 2008 in order to facilitate both retrospective and prospective clinical trials of radiosurgery performed with the same delivery platform. The consortium has published retrospective clinical trials related to cluster headache, glomus tumors, chordoma, and non-functioning pituitary tumors. Completed retrospective clinical trials related to chondrosarcoma and hemangioblastomas were submitted. Trials in accrual include posterior fossa meningiomas, repeat AVM radiosurgery, meningioma edema, and pineal region tumors. Prospective clinical trials include NAGKC 12-01 (outcomes for more than five brain metastases using a neurocognitive and tumor control endpoints, PI Igor Barani, UCSF) and NAGKC 12-02 (malignant glioma, radiosurgery plus bevacizumab, a phase II clinical trial, PI Ajay Niranjan, UPMC) funded by a combination of external and internal sources.

Ongoing Studies:

NAGKC 12-01 Randomized controlled study of outcomes in patients with five or more brain metastases update:
a study of cognition in patients with 5+ Metastases
PI Igor J. Barani, M.D

NAGKC 12-02: Multicenter Phase II Study of Border Zone Stereotactic Radiosurgery with Bevacizumab in Patients with Recurrent or Progressive Glioblastoma Multiforme
PI Ajay Niranjan MBA Hideyuki Kano MD, PhD Edward Monaco III, MD, PhD John C Flickinger MD, L. Dade Lunsford MD
STUDY TYPE: Interventional
STUDY DESIGN: Single-arm, one-stage phase II trial
ALLOCATION: Non-Randomized
ENDPOINT CLASSIFICATION: Safety/Efficacy Study
MASKING: Open Label Primary Purpose: Treatment Patient
NUMBERS: 40
INDICATION: Recurrent or Progressive GBM
HYPOTHESIS: ‘Border zone’ of GBM is defined as MRI volume of enhancement plus up to 2 cm of the surrounding T2 volume. This represents the volume of tumor infiltrated white matter and is the route of GBM spread.
HYPOTHESES:
1. GBM is a “local” disease
2. Failure to eradicate tumor cells in the migration pathways (the “border zone”) leads to tumor progression.
3. Survival will improve if SRS target volume includes the “border zone”
4. Bevacizumab, a monoclonal antibody to VEGF, has been approved for GBM.
5. SRS + BVZ will be an effective strategy for GBM (BVZ will maximize the effects of radiation in the treated volume and potentially reduce radiation toxicity in the adjacent brain)

NAGKC 13-01 Radiosurgery or Open Surgery for Epilepsy (ROSE)
• Phase 3 trial comparing temporal lobectomy with radiosurgery – 14 U.S. sites, 2 India, 2 U.K.
• Randomized comparison of 234 cases
• Large number required to show “non-inferiority”
• Six years with primary aim seizure-freedom in third follow-up year
• Radiosurgery requires an average of 1 year for initial response
• Definition of seizure-free is 12 consecutive months with no seizures
**PROCEDURE**

- After a treatment plan is developed, it will be transferred electronically to UCSF for review and approval.
- Amygdala, anterior 2 cm of the hippocampus, parahippocampal gyrus will be included in the radiosurgical target (volume to range from 5.5-7.5).
- Patients will receive 24Gy to the 50% isodose line using an unlimited number of isocenters (likely to range from six to 30).
- Brainstem/ON 10Gy/8Gy

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**French Prospective Trial in Progress**

**Gamma Knife Subthalamotomy for Parkinson’s Disease: A Prospective Trial.**

*Pl Jean Régis, Tatiana Witjas, Romain Carron, Jean Philippe Azulay*

- Stereotactic thermocoagulation of the STN may induce significant and long-lasting results (Alvarez et al. 2005 & 2009).
- Intranuclear lesion is associated with no or only mild dyskinesia (Guridi & Obeso, Brain 2001)

**UPDATE:** 1st inclusion: 14 February 2011

**END OF THE INCLUSIONS:** 31 December 2013

**1ST TREATMENT:** 15 February 2011

**NUMBER OF PATIENTS INCLUDED DECEMBER 31, 2013:** 14 (initial goal 20 patients)

**NUMBER OF PATIENT UNDER FU:** 11

**AT THIS DATE:**

- 4 patients got GK1 + GK2 at 12 months
- 1 patient got GK2 at 15 months from GK1
- 2 patients still waiting for GK2 at 18 & 21 months from the first GK
- 1 patient, completing is FU with only one side treated.

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**Japanese Leksell Gamma Knife (JLGK) Study Group**

**JLGK1101 Retrospective study of symptomatic cavernous angioma.**

*Pl: Yoshihisa Kida (submitting)*

334 cases from 23 facilities.

**JLGK1201 Retrospective study of central neurocytoma.**

*Pl: Kazuhiro Yamanaka (submitting)*

36 cases from 23 facilities.

**CUMULATIVE LOCAL CONTROL:** 95%/5 years, 86%/10 years.

**CUMULATIVE PROGRESSION-FREE RATES (INCL DISTANT LESIONS):** 88%/5 years, 64%/10 years.

Neither pre-SRS clinical factors nor radiosurgical parameters were shown to correlate to progression-free survival. Symptomatic tumor hemorrhage and adverse radiation effect occurred in one patient each.

**JLGK1302 Retrospective study of jugular foramen schwannomas.**

*Pl: Toshinori Hasegawa (recruiting cases)*

117 cases from 17 facilities.

**JLGK1303 Retrospective study of craniopharyngioma.**

*Pl: Tatsuhiko Tsugawa (analyzing data)*

286 cases from 15 facilities.

**JLGK1401 Retrospective study of brain metastases**

*Pl: Masaaki Yamamoto (recruiting cases)*

74 cases from 18 facilities as of May 06, 2014.
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18. Arjun Sahgal: Sunnybrook Health Sciences Center - Toronto OC. OVERALL SURVIVAL ADVANTAGE FOR SRS ALONE VS. WBRT PLUS SRS IN PATIENTS AGE 50 AND YOUNGER 2014.


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72. Qingsheng Xu: Department of Neurosurgery tFAH-H, China. GAMMA KNIFE SURGERY FOR BRAIN METASTASES FROM HEPATOCELLULAR CARCINOMA 2014.

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84. Shunya Hanakita: The University of Tokyo Hospital - Tokyo J. RADIATION INHIBITION OF REDUCTION OF CEREBRAL ARTERIOVENOUS MALFORMATIONS 2014.

85. Mooseong Kim: Inje University Busan Paik Hospital - Busan SK. EMBOLIZATION WITH GAMMAKNIFE SURGERY OF GIANT INTRACRANIAL ARTERIOVENOUS MALFORMATIONS 2014.

86. Michele Longhi: AUO Verona - DPT Neurosurgery - Verona I. LGK FOR PEDIATRIC AND ADOLESCENT CAVMs RESULTS ON 100 CASES FOLLOWED UP FOR AT LEAST 36 MONTHS 2014.


89. Michele Longhi: AUO Verona - DPT Neurosurgery - Verona I. LGK FOR PEDIATRIC AND ADOLESCENT CAVMs RESULTS ON 100 CASES FOLLOWED UP FOR AT LEAST 36 MONTHS 2014.

90. Shunya Hanakita: The University of Tokyo Hospital - Tokyo J. STEREOTACTIC RADIOSURGERY FOR ARTERIOVENOUS MALFORMATIONS IN CHILDREN (<15 YEARS OLD) 2014.

91. Daniel Tonetti: University of Pittsburgh Department of Neurologica - Pittsburgh PU. HEMORRHAGE FROM AVMS DURING PREGNANCY IN THE LATENCY INTERVAL AFTER STEREOTACTIC RADIOSURGERY 2014.


100. Josa Frischer: Medical University Vienna - Vienna A. EVALUATION OF TREATMENT OPTIONS FOR BRAINSTEM CAVERNOUS MALFORMATIONS: A SINGLE CENTRE EXPERIENCE 2014.


120. Cheng-Siu Chang: Chang Bing Show Chwan Memorial Hospital - Changhua County T. IMPACT OF RADIATION DOSE ON OUTCOME IN ACOUSTIC NEUROMA TREATED WITH GAMMA KNIFE SURGERY 2014.


122. Constantin Tuleasca: Lausanne University Hospital/ University of Lausanne S. COMBINED APPROACHES IN LARGE VESTIBULAR SCHWANNOMAS: SINGLE AND MULTI-FRACTION RADIOSURGERY OUTCOMES IN THE TREATMENT OF VIII NERVE SCHWANNOMAS 2014.

123. Motohiro Hayashi: Department of Neurosurgery, Tokyo Women's Medical University - Tokyo J. HEARING PRESERVATION AFTER ROBOTIC GAMMA KNIFE MICRORADIOSURGERY FOR VIII NERVE SCHWANNOMAS 2014.


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INDICATIONS TREATED
1968 TO 2013

Leksell Gamma Knife

68%-100% of sites reporting
Treatments by Indication Category

Cumulative Number of Patients Treated by Indication Category

Number of Patients Treated by Indication Category

Relative Distribution of Indications Per Year
Benign Tumors Treated

Benign Tumors - Cumulative Number of Patients Treated Per Year

Benign Tumors - Number of Patients Treated Per Year

Benign Tumors - Cumulative Number of Patients Treated by Indication

Meningioma 112.7 thous.
Vestibular Schwannoma 77.7 thous.
Pituitary Adenoma 59.2 thous.
Other Indications 45.9 thous.
Leksell Gamma Knife
Indications Treated 1968 to 2013

Functional Disorders Treated

Functional Disorders - Cumulative Number of Patients Treated Per Year

Functional Disorders - Number of Patients Treated Per Year

Functional Disorders - Cumulative Number of Patients Treated by Indication

- Trigeminal Neuralgia: 52.1 thous.
- Epilepsy: 2.8 thous.
- Parkinson’s Disease: 1.9 thous.
- Other Indications: 3.0 thous.
Malignant Tumors Treated

Malignant Tumors - Cumulative Number of Patients Treated Per Year

Malignant Tumors - Number of Patients Treated Per Year

Malignant Tumors - Cumulative Number of Patients Treated by Indication

Indication (thous.)
- Metastatic Tumor
- Malignant Glial Tumor (grade II-IV)
- Other Malignant Tumor
- Other Indications

- 305.6 thous.
- 33.6 thous.
- 12.1 thous.
- 3.3 thous.
Leksell Gamma Knife
Indications Treated 1968 to 2013

Vascular Disorders Treated

Vascular Disorders - Cumulative Number of Patients Treated Per Year

Vascular Disorders - Number of Patients Treated Per Year

Vascular Disorders - Cumulative Number of Patients Treated by Indication

Indication (thous.)

AVM 81.6 thous.
Cavernous Angiomas 8.7 thous.
Other Vascular Disorder 5.7 thous.
Aneurysms 0.7 thous.
Treatments by Indication and Region

Indication Category Distribution by Region

Accumulated Treatments by Region and Indication

Indication Category Distribution by Region

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<th>Indication Category</th>
<th>Indication</th>
<th>Asia excl. Japan</th>
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(2013 Average Treatments per Site: 261)

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Treatments by Region - Europe

Europe - Cumulative Number of Patients Treated Per Year

Europe - Number of Patients Treated Per Year

Europe - Cumulative Number of Patients Treated by Indication

Indication Category (thous.)
- Benign Tumors: 76.2 thous.
- Malignant Tumors: 52.4 thous.
- Vascular Disorders: 26.4 thous.
- Functional Disorders: 23.2 thous.
- Other Indications: 9.8 thous.

Treatments by Region - Europe
Leksell Gamma Knife
Indications Treated 1968 to 2013
Treatments by Region - Japan

Japan - Cumulative Number of Patients Treated Per Year

Japan - Number of Patients Treated Per Year

Japan - Cumulative Number of Patients Treated by Indication

Indication Category (thous.)
- Malignant Tumors 141.0 thous.
- Benign Tumors 39.2 thous.
- Vascular Disorders 14.8 thous.
- Other Indications 4.9 thous.
Treatments by Region - Latin America

Latin America - Cumulative Number of Patients Treated Per Year

Indication Category
- Ocular Disorders
- Functional Disorders
- Malignant Tumors
- Vascular Disorders
- Benign Tumors

Latin America - Number of Patients Treated Per Year

Indication Category
- Ocular Disorders
- Functional Disorders
- Malignant Tumors
- Vascular Disorders
- Benign Tumors

Latin America - Cumulative Number of Patients Treated by Indication

Indication Category (thous.)
- Benign Tumors: 1.9 thous.
- Vascular Disorders: 1.5 thous.
- Malignant Tumors: 1.0 thous.
- Functional Disorders: 0.3 thous.
- Other Indications: 0.1 thous.
Treatments by Region - Middle East & Africa

Middle East & Africa - Cumulative Number of Patients Treated Per Year

Middle East & Africa - Number of Patients Treated Per Year

Middle East & Africa - Cumulative Number of Patients Treated by Indication

Indication Category (thous.)
- Benign Tumors: 10.1 thous.
- Vascular Disorders: 2.3 thous.
- Malignant Tumors: 1.9 thous.
- Functional Disorders: 0.6 thous.
- Other Indications: 0.0 thous.
Leksell Gamma Knife
Indications Treated 1968 to 2013

Treatments by Region - North America

North America - Cumulative Number of Patients Treated Per Year

North America - Number of Patients Treated Per Year

North America - Cumulative Number of Patients Treated by Indication

Indication Category (thous.)
- Malignant Tumors 99.7 thous.
- Benign Tumors 59.1 thous.
- Functional Disorders 33.2 thous.
- Vascular Disorders 15.9 thous.
- Other Indications 0.1 thous.