Stereotactic gamma knife radiosurgery in the treatment of brain metastases

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Introduction
Annually, about 4,300 patients per million people present with cancer; according to conservative estimates about 8% of these patients will develop brain metastases. Cerebral metastases are frequently responsible for the leading symptoms in cancer; their local control is particularly important for the patient’s quality of life and survival. So far, fractionated whole brain radiotherapy has been the standard therapy for patients with brain metastases, but recently serious shortcomings have become evident; several large studies demonstrated a very limited impact of fractionated radiotherapy on the patient’s prognosis with a median survival between 2.8 and 3.4 months. The local control of brain metastases is unsatisfactory after fractionated whole brain radiotherapy (WBRT) with complete or partial responses in only 24-55%. Six months after radiotherapy, colorectal cancer metastases showed a local control of 17% after 10 Gy. Metastases from malignant melanoma or renal cancer typically do not respond to fractionated radiotherapy with resulting local control rates of 0% and 7% after 12 months after a typical fractionated radiation treatment with 3 Gy × 10.

One important argument for fractionated whole brain radiotherapy has been the intended treatment of the microscopic disease in multiple metastases and the prevention of future distant brain metastases. Unfortunately, this is not the case, as Aoyama showed in a randomised controlled trial that the 12-month actuarial rate of developing new brain metastases was 41.5% in the group of patients who had been treated with whole brain radiotherapy (in addition to radiosurgery). Others report new remote metastases in 34% and more. Short-term memory deficits appear relatively early after whole brain radiotherapy and many patients are concerned by the hair loss.

These inherent drawbacks of conventional fractionated radiotherapy of brain metastases led to a worldwide shift of interest towards radiosurgical results. Radiosurgery has shown that a physically focused and stereotactically applied radiation can overcome many biological limitations of fractionated radiotherapy. The consequence is the worldwide increasing acceptance of gamma knife with more than 450,000 treated patients.

The need for minimal invasive approaches, shorter hospitalisation and outpatient treatment options have been pointed out in many medical fields. A recent review of the literature the European Federation of Neurological Societies (EFNS) and the resulting guidelines mark an important paradigm shift in the treatment of brain metastases; while the value of a surgical tumour resection for larger metastases with mass effect is still emphasised, stereotactic radiosurgery is recommended in patients with smaller brain metastases with a diameter of less than 3cm or tumours located in eloquent cortical areas, basal ganglia and brain stem or with comorbidities precluding surgery. Only the remaining patients not amenable to surgery or radiosurgery are recommended to undergo fractionated whole brain radiotherapy.

Gamma knife radiosurgery
The principle of radiosurgery is based on concentrating radiation within the tumour without irradiating the surrounding healthy tissue. The gamma knife achieves this by mechanical focusing of ca 200 radiation sources which allows a sophisticated shaping of an extremely confined irradiated volume in the brain. With modern gamma knife techniques and multiple isocentres, virtually any geometrical structure, i.e. any shape of a tumour, can be matched with high precision radiation and a very steep radiation dose fall-off. The normal brain tissue surrounding the tumour is exposed to only very little radiation and thereby “protected” against undesired radiation effects.

Other stereotactic radiation technologies achieve a similar physical concentration of radiation using technical solutions based on the linear accelerator (linac) technology. In the stereotactic linac the radiation beam is shaped by an individually adapted array, the multi-leaf collimator. The Cyber Knife allows shaping of the radiation target using a small accelerator that is mounted on a robot arm that irradiates the target from various angles. The gamma knife seems to allow the steepest radiation gradient and the lowest irradiation of normal tissue, but the discussions concerning the accuracy of the various radiosurgical techniques did not result in scientifically documented differences in clinical outcome.

The necessary precision requires a stereotactic MRI or CT study before radiosurgery and a stereotactic frame fixation during treatment (for linac and gamma knife). Radiation doses are expressed as “minimum doses” or “prescription doses” reflecting the dose applied to the tumour periphery. Generally, prescription doses of 18-22 Gy are applied in radiosurgical treatment of cerebral metastases. This minimum dose concept defines a threshold dose for the clinical local efficacy and results in an inhomogeneous dose distribution with a maximum dose within the tumour ranging between 20 and 50 Gy. It has been shown that this lack of dose homogeneity is irrelevant for the outcome.

Local tumour control after radiosurgery
More than 141,000 patients with brain metastases have been treated so far with gamma knife radiosurgery. A wide range of retrospective and a few prospective studies with more than 4,800 published patients with radiosurgically-treated brain metastases provide consistent and reproducible results with an average local tumour control between 84 and 97%.

Gamma knife radiosurgery is highly effective even for melanoma and renal cell cancer metastases that are otherwise resistant to conventional fractionated external beam radiation therapy.

Three retrospective and one recent prospective randomised study compared the efficacy of radiosurgery of brain metastases with the combined effect of open microsurgery plus WBRT. Treatment results were similar in terms of survival, neurological death rates and freedom from local recurrence. Radiosurgery was associated with a shorter hospital stay, less frequent and shorter timed steroid application, and lower frequency of toxicities. For smaller metastases, the therapeutic effect of gamma knife radiosurgery can therefore be considered as equivalent to surgical approaches.

Recently, a randomised prospective study was published showing that patients receiving stereotactic radiosurgery alone were at a significantly lower risk of an early significant decline in learning and memory function compared with the group that received additional fractionated whole brain radiotherapy. A recent prospective randomised study docu-
ments a benefit for functional stability and quality of life for radiosurgically treated patients. In this study, the outcome after conventional radiotherapy was compared with patients receiving an additional radiosurgical boost. After radiosurgery, patients will not experience hair loss. Clinical results are similar for the various radiosurgical techniques.

Since radiosurgery is a local treatment, a prophylactic effect against potential future brain metastases cannot be expected.3 Radiosurgically treated patients will experience new remote metastases outside the treatment area in 39%-52%. After fractionated whole brain radiotherapy 34-41% of patients will develop new metastases.1,3,8

WBRT cannot be repeated in case of new remote metastases, while another session of radiosurgery is generally possible due to the spatially limited radiation effect. Conventional fractionated radiotherapy does not seem to provide a prophylactic benefit as an addition to radiotherapy. Several recent studies comprising more than 1,059 radiosurgically treated patients have not documented any differences in survival when fractionated whole brain radiotherapy was omitted.3,11,14,45 It is, however, important to note that WBRT and radiosurgery can be combined if necessary. Stereotactic radiosurgery can be applied for tumour recurrences after conventional fractionated radiotherapy, as WBRT can be given in case of a more general cerebral tumour spread after radiosurgery.

Initial tumour control after gamma knife radiosurgery is not affected by the number of brain metastases. Treatment recommendations that are related to the number of metastases have potential dramatic consequences, since hereby a considerable amount of patients are declined specific therapy although their metastases could be treated. There is increasing scientific evidence to the high efficacy of radiosurgery even for patients with multiple (>4) brain metastases. Patients with single metastases seem to have a slightly better prognosis, but for patients with multiple metastases there is no simplistic relation between number of brain metastases and survival.

The American Society for Therapeutic Radiology and Oncology (ASTRO) stated, after an evidence-based review of the role of radiosurgery for brain metastases, that the addition of radiosurgery boost to WBRT improves brain control as compared with whole-brain radiotherapy alone.4 It is important to remember that most treatment recommendations are based on level I evidence and hence on the available randomised studies. These have all limited the number of treated metastases (<4) in the study’s inclusion criteria and therefore not tested the outcome for a higher number of metastases. However, multiple retrospective studies do not show evidence for an inferior treatment specific outcome after radiosurgery of multiple metastases. It is also important to note that the patient’s outcome depends primarily on the systemic disease. Improvements in systemic cancer therapies require higher standards in the treatment of brain metastases than are so far available with conventional whole brain radiotherapy. During radiosurgery chemotherapy does not have to be interrupted, so valuable time is gained for the patient’s systemic cancer therapy. Significant advantages in mental status and quality of life support the use of radiosurgery.

Adverse radiation effects (ARE) are considered the most important limiting factors in radiosurgery of cerebral metastases. Adverse radiation effects generally present as secondary oedema and/or increase of contrast enhancement several months after radiosurgery. When the oedema appears within an eloquent region, the ARE can result in neurological dysfunctions often treated with steroids. Dose volume statistics showed a significant relation between the occurrence of ARE and the volume of the peripheral isodose. Therefore, tumours larger than a volume of 8-10cc should not be treated with radiosurgery.

Treatment of brain metastases should be effective against the current dominant symptoms and focused on the patient’s quality of life; the treatment should not be time-consuming or inappropriately invasive and should allow the continuation of the systemic therapy. The gamma knife fulfills these requirements.

**References**


