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**Author:** Wiggenraad, Ruud  
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SUMMARY
Stereotactic radiotherapy (SRT) is an important treatment modality for patients with intracranial tumors. The main characteristic of SRT is its high level of accuracy that enables very precise and effective treatment of these tumors, thereby avoiding damage to the delicate and vulnerable surrounding normal tissue. RCWEST started performing SRT in 2004 on the Novalis, a dedicated linear accelerator. Shortly afterwards a specialized SRT team was formed. Technical and clinical issues concerning the SRT program were discussed on a weekly basis. During these discussions several questions and ideas were raised concerning treatment techniques and the clinical results of SRT. These questions were the starting point of our studies about SRT of intracranial tumors. This thesis describes seven studies we did looking for optimal treatment techniques and looking for improved understanding of the clinical effects of SRT of tumors in the brain.

Chapter 1 is a general introduction, describing the history of radiosurgery and SRT and the development of these modalities towards contemporary SRT. Radiosurgery and SRT nowadays have many common characteristics, but both treatment modalities had a very different history. The idea of stereotactic radiosurgery was developed by the Swedish neurosurgeon Leksell. He coupled an X-ray tube to a stereotactic frame in order to very accurately produce a lesion in the brain with a single high radiation dose. This method to produce a lesion in the brain was considered a surgical procedure and therefore branded as radiosurgery. In later years the techniques of radiosurgery were improved and new indications were developed, such as tumor treatments. However, the basic idea of the neurosurgeons about radiosurgery remained the same, i.e. a method for tissue destruction using a single high radiation dose. With the invention of linear accelerators and the development of radiation oncology as a medical specialty, it also became possible for radiation oncologists to perform stereotactic treatments. Radiation oncologists, however, had their radiobiological background and had experience with fractionated treatments. Therefore, they did not only apply single fraction treatments as the neurosurgeons did, but also started to explore the value of fractionated stereotactic treatments. As many of them considered these treatments a form of radiotherapy, the term stereotactic radiotherapy was introduced. Nowadays, there are a variety of techniques in the field of stereotactic treatments. A stereotactic frame is no longer mandatory, because image based radiotherapy can be as accurate as frame-based treatment. We define cranial SRT as an external beam method to very precisely deliver a radiation dose to an intracranial target via stereotactic guidance or image guidance in either a single fraction or in multiple fractions. Finally, we consider radiosurgery as equivalent to single fraction SRT.

Chapter 2 consists of two technical studies aiming at optimizing the treatment. Chapter 2a reports the results of a comparative SRT planning study. SRT treatment plans were made for 25 patients with either a glioma or meningioma. For all patients plans were made using Dynamic Conformal Arc (DCA), a forward planning technique, and Intensity Modulated Radiotherapy (IMRT), an inverse planning technique. The plans were evaluated using a set of pre-defined criteria. We found that acceptable treatment plans were possible using both DCA and IMRT. Tumour type, size, or shape did not predict a preference for a DCA or IMRT plan. Preference for one of the two techniques was in some cases based on differences in conformity index, homogeneity index or dose in a predefined critical structure. In most cases however, there was no clear difference. Since then we have favoured DCA over IMRT in the majority of cranial SRT patients because of its shorter delivery time and less time-consuming quality assurance checks.

Chapter 2b reports the results of a study about patient fixation for SRT. Optimal fixation of the patient is essential for the accurate delivery of cranial SRT. When the SRT program started, we used the standard relocatable frame with the Brainlab mask system to which an
upper jaw support (UJS) was added to improve the immobilization. Based on measurements using the Brainlab Exactrac system we concluded that there was room for improvement of the patient fixation. In our department an adaptor to the Brainlab mask system was developed to which a vacuum mouthpiece (VMP) could be attached. In this study we compared the positioning accuracy before and after treatment in 20 SRT patients who were immobilized using the UJS to the accuracy in 20 SRT patients who were immobilized using the VMP. We found that using the VMP resulted in smaller interfraction rotations and smaller intrafraction translations and rotations. Our conclusion was that the VMP resulted in better patient fixation and smaller rotations compared to the UJS. Since we have found these results we use the VMP in all cranial SRT patients in whom the dentition allows its application and the UJS in the remaining patients.

Chapter 3 consists of three clinical studies about the outcome after SRT of brain metastases. In chapter 3a the effects of SRT are reported in the first cohort of 86 patients with brain metastases, treated between July 2004 and January 2007 with our department’s Novalis linac. The median survival of the whole patient group was 6.2 months. Prognostic factors for overall survival were Karnofsky Performance Score (KPS) and gender. Median survival times of patients with a KPS ≥90 versus <90 were 9.5 months versus 3.9 months respectively. Therefore, patients with a good performance status are more likely to live long enough to benefit from SRT than patients with a worse performance status. Prognostic factors for local tumor control were KPS and SRT dose. An important result of this study was the disappointing local control rate (37% at 12 months) of large metastases treated with one fraction of 15 Gy. Methods to improve the local control rate of these large metastases were discussed, such as surgery and fractionated stereotactic radiotherapy (FSRT). In this cohort only conventional MRI scans and FDG-PET scans were applied if radiation necrosis was suspected. In 6% of the irradiated lesions radiation necrosis was considered certain.

We decided that fractionated SRT (FSRT) would be indicated to improve local control of large brain metastases. We chose the 3x 8Gy scheme, because the Biologically Equivalent Dose (BED) model suggested this prescription would be safe and could possibly improve local control. At the same time we decided to do a literature review to collect the evidence concerning the relation between SRT dose and local control probability.

In chapter 3b we describe this review. We studied the literature, published from 1990 through 2009, on the results of SRT of brain metastases. In only 11 out of the 260 published papers a relation between dose and local control could be derived. We found in the studied literature that local control after single fraction SRT was highly dependent upon dose. One-year local control rates were higher than 80% with doses ≥ 21 Gy, higher than 60% with doses ≥ 18 Gy and lower than 50% with doses ≤ 15 Gy. One-year local control rates after the published FSRT schemes were all 70% or higher and were dependent on dose as well. Based on an analysis of the available data we could define a BED that should at least be prescribed in order to enable a one-year local control rate of 70%. This BED corresponds with a single fraction of 20 Gy, two fractions of 11.6 Gy or three fractions of 8.5 Gy. It was not possible to draw conclusions concerning a relation between dose, irradiated volume and radiation necrosis.

In chapter 3c the results of FSRT (3x 8Gy) are reported in a second cohort of patients treated in our department from September 2007 through September 2009. This cohort only contained patients who received FSRT for one of the following two reasons: PTV size > 13cm³ or brainstem location. The local control rates in these patients were, retrospectively, compared with the results in patients from the first cohort with the same tumor characteristics who had received 15Gy in one fraction. With all known shortcomings of a retrospective comparison
and the small patient numbers the conclusion was that the fractionated scheme of 3x 8Gy was not clearly superior to 15Gy single fraction. One-year local control rates were below 70% with both SRT schemes. Moreover, perfusion MRI became available for patients with a growing lesion after SRT to differentiate tumor progression from pseudo-progression, which is an often self-limiting manifestation of radiation toxicity. One-year pseudo-progression rates were not significantly different after 15Gy (15%) and 24Gy (25%). We concluded that FSRT schemes with a higher biological equivalent dose would be necessary to improve local control rates. This was in line with the conclusion of chapter 3b. Moreover, the studies in chapter 3 raised questions about the occurrence and the nature of pseudo-progression in these patients.

Chapter 4 consists of two studies looking further into the problem of the growing lesion after SRT of brain metastases.

Chapter 4a deals with the nature of the pseudo-progressive lesion. In this chapter the question is raised whether the lesion growth is caused by an enlargement of the metastasis or by contrast enhancement in the surrounding normal brain tissue. To improve our understanding of this phenomenon we made cine-loops from series of co-registered follow-up MRI scans. These cine-loops quite convincingly showed a similar course of events in the 10 patients we studied. We concluded that probably this pseudo-progression is a radiation effect on the surrounding normal brain tissue and not on the metastasis itself.

Chapter 4b aims to describe what happens clinically in patients with a pseudo-progressive lesion or local tumor progression. We studied the clinical course of 65 patients with 85 growing lesions after SRT of brain metastases. The majority of these patients had perfusion MRI scans included in their follow-up. Pseudo-progression was diagnosed in 59% and tumor progression in 11% of the growing lesions and in 30% the cause of the progression could not be determined. Neurological symptoms occurred in 70% of the patients with pseudo-progression and in 100% of the patients with tumor progression. Four patients (44%) with tumor progression improved after resection of the progressive tumor. In 51% and 56% of patients with pseudo-progression and tumor progression respectively, neurologic symptoms did not improve. Thirty-five percent of the patients with pseudo-progression became asymptomatic. We concluded that patients with symptomatic pseudo-progression remained or became asymptomatic.

In chapter 5 the main findings are discussed and future perspectives formulated.

In chapter 5 the main findings are discussed and future perspectives formulated. The two technical studies deal with treatment planning and patient fixation. We found that acceptable treatment plans were possible using DCA or IMRT. However, more sophisticated techniques such as volumetric modulated arc therapy (VMAT) and single isocenter dynamic conformal arcs (SIDCA) are being incorporated into the practice of SRT. The main advantage of these new techniques is the reduced treatment time, especially for SRT patients with multiple brain metastases. The merits of proton treatment compared to photon SRT in patients with intracranial tumours still have to be determined. The importance of patient fixation is not changing, although patient positioning will be more and more image based and treatment times will be reduced. Therefore, the VMP will remain an important tool for patient fixation.

The clinical studies deal with the relation between SRT dose and local control and with late radiation effects in patients with brain metastases. We have defined a biologically equivalent dose needed for a one-year local control rate of at least 70%. Although we can be confident
that a single fraction dose of at least 20Gy is needed for adequate local control, more clinical results are needed to confirm our calculations concerning fractionated schemes in the clinic. We have reported that pseudo-progression after SRT of brain metastases can cause irreversible neurologic damage. To reduce the rate of pseudo-progression the size of the CTV-PTV margins should be reconsidered. There are indications that by reducing these margins local control rates are not affected, but pseudo-progression rates can be smaller. In the nearby future uniform dose prescription and reporting will be necessary. More patients with brain metastases will be eligible for SRT, notably selected patients presenting with four to ten brain metastases and patients who had an irradical resection of a brain metastasis. Finally, we argued that radiation oncologists should be involved in the follow-up after SRT of brain metastases.

CONCLUSIONS

In this thesis we showed that treatment planning for SRT of patients with intracranial tumors is optimal using both DCA and IMRT. Patient fixation is improved by adding a vacuum mouthpiece to a frame based fixation system. SRT produces excellent local control results in most patients with small brain metastases. A minimum BED was determined that would be needed for a 1-year local control rate of at least 70% after SRT of large brain metastases. Fractionated SRT is needed for safe administration of such higher biological equivalent doses. Lesion growth after SRT of a brain metastasis can be caused by radiation toxicity of normal brain tissue. This pseudo-progression can be symptomatic or asymptomatic. Patients with symptomatic pseudo-progression or local tumor progression after SRT have a similar clinical course. Therefore, symptomatic pseudo-progression should be regarded as serious radiation toxicity. Reduction of the pseudo-progression rate is possible if SRT is performed without CTV-PTV margin. Radiation oncologists should be involved in the follow-up after SRT of brain metastases.