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**Title:** Stereotactic radiotherapy of intracranial tumors: optimizing treatment and improving outcome  
**Issue Date:** 2016-02-10
CHAPTER 5

Discussion
and future perspectives
DISCUSSION

We define Stereotactic Radiotherapy (SRT) as an external beam method to very precisely deliver a radiation dose in either a single fraction or in multiple fractions via stereotactic guidance or image guidance.

This thesis consists of two types of studies. Two technical studies aim at optimizing the delivery of SRT of intracranial tumors. Five clinical studies deal with SRT in brain metastases and aim at improving treatment outcome.

I: TECHNICAL STUDIES, CHAPTER 2

TREATMENT PLANNING

A high dose conformity with a sharp dose fall-off outside the PTV is an important characteristic of SRT. The treatment machine has to meet stringent requirements to make this possible, but the quality of the treatment plan is essential as well. Chapter 2a reports the results of an SRT planning study of intracranial tumours comparing Dynamic Conformal Arc (DCA), a forward planning technique, and Intensity Modulated Radiotherapy (IMRT), an inverse planning technique.

We found that using both techniques acceptable treatment plans were possible. 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. In these patients we favoured DCA over IMRT because of its shorter delivery time and less time-consuming quality assurance. Contrary to our expectation the shape of the PTV did not predict what technique would enable a better plan. For concave tumours excellent DCA plans could be made. However, the quality of a DCA plan relies more on the experience and the skills of the individual planner than the quality of an IMRT plan.

In recent years we have seen a rapid introduction in the clinic of more sophisticated rotational techniques that combine rotation of the gantry with intensity modulation [1]. The use of these volumetric modulated arc therapies (VMAT) has already been incorporated into the practice of SRT [2]. The quality of the VMAT plans is comparable to that of classic SRT plans [3]. As main advantage of VMAT has been reported the shorter delivery time [4]. The beam-on time can even be decreased further by using flattening filter free (FFF) beams [5]. However, VMAT and DCA techniques both need multiple table positions for an acceptable plan quality [6]. The reported treatment time is usually at least in the order of 20 minutes. Patient positioning and changing table positions take the largest part of this treatment time. Therefore, in SRT cases with a single target, a reduction in beam-on time in the order of 5 minutes or less when using VMAT with FFF will not have a dramatic influence on total treatment times compared to DCA [6,7]. Moreover, the efficacy of these newly developed SRT techniques has not been proven to be better when compared to the classical techniques such as DCA and Gamma Knife.

In patients with multiple brain metastases the indication for SRT has classically been restricted to patients with 1-4 lesions. Some hospitals, mainly centres using a Gamma Knife (Elekta AB, Stockholm, Sweden), have traditionally been using SRT in patients with even more than 4 brain metastases. A recent publication has raised the interest for using SRT for this new category of patients more widely [8]. However, treating each metastasis with a separate isocenter is time consuming and hence cumbersome for the patients and the radiotherapy departments. Therefore the introduction of new techniques that enable the use
of a single isocenter is an improvement for this particular group of patients. VMAT is an efficient single isocenter technique for SRT of multiple brain metastases. VMAT and single isocenter dynamic arcs (SIDCA) have been compared with the classic multiple isocenter dynamic conformal arc (MIDCA) technique for multiple brain metastases using Eclipse (Varian, Palo Alto, USA) [9]. The advantage of VMAT was the shortest treatment time, but the dose in normal brain tissue was lowest with SIDCA and MIDCA. SIDCA may therefore be regarded as an excellent linac SRT technique for patients with a limited number of brain metastases. Another SIDCA technique (Automatic Brain Metastases Planning) has recently been introduced by Brainlab (Brainlab, Feldkirchen, Germany). There are conflicting data in the literature about the merits of VMAT compared to Gamma Knife for SRT of multiple brain metastases, especially with respect to the dose in the normal brain. Some authors report a lower dose in the brain using the multiple isocenter Gamma Knife technique [10,11]. Another author reports equivalent plan quality, including normal brain dose, and a considerable reduction in treatment time using a 4 arc VMAT technique planned in Eclipse [12]. Based on the available literature the preferred SRT techniques for multiple brain metastases will probably be single isocenter techniques based on VMAT or DCA. The plan quality of multiple isocenter techniques seems to be equivalent, but these techniques need more treatment time and, therefore, are less efficient.

Another development in the field of high precision treatment of brain tumours is the renewed interest in proton treatment. Although this modality is not new (protons were used earlier than high energy photons for stereotactic radiotherapy) the latest technical developments and the establishment of new proton centres have raised this new interest. Spot scanning proton therapy is becoming the new standard because the high-dose conformality is reported to be better [13]. Many consider protons the treatment of choice for chordomas and chondrosarcomas of the skull base, although not all authors agree on this [14,15]. The main advantage of proton therapy seems to lie in the intermediate and low dose regions, making it an attractive option in the treatment of paediatric tumours. The main reason is the expected lower rate of secondary tumours in children. However, the long-term risks of proton therapy have not yet been assessed [16]. Another advantage lies in the ability to decrease doses in structures that are not in the immediate vicinity of the CTV, such as the hippocampi and vascular structures in craniopharyngioma patients [17].

Presently proton therapy and SRT do not seem to share the same advantages. The advantage of protons in comparison to photons only lies in the steeper dose fall-off at the end of range of proton beams. The advantage of stereotactic photons can be found in the sharp dose fall-off in the high dose regions enabled by the highly accurate set-up and by different beam properties such as the smaller penumbra.

Probably the possibilities of stereotactic photons and protons will in the future remain complementary. The practice of SRT with photons is becoming more and more efficient. [7,18,19].

**PATIENT FIXATION**

For high precision radiotherapy adequate patient fixation is an absolute requirement. In chapter 2b we examined the additional value of a vacuum mouthpiece to the standard Brainlab mask system. We concluded that adding the mouthpiece resulted in better patient fixation, making it a useful addition to the mask system. Using the mouthpiece the intrafraction patient movements were extremely limited, leaving virtually no room for further improvement of this combined fixation system. The fixation system we used is based upon a stereotactic frame, to which a localiser box can
be attached. In this way fixation and stereotactic localisation are combined. At present, however, in a growing number of linac SRT departments the isocenter is not positioned based on a stereotactic coordinate system, but based on on-line imaging. For linac based SRT so-called frameless SRT is becoming the standard. Therefore new fixation systems have been developed. The main concern in the evaluation of these fixation systems is the occurrence of intrafraction movement. Even the fastest 4 arc FFF VMAT techniques are reported to take 12–22 minutes [12]. This time duration and the necessary table position changes may allow for intrafraction movements. Two strategies can be used to deal with this source of inaccuracy. One is to correct the position after each table position change by repeated position verifications. This strategy is described in a recent paper from a department in which SRT is applied with multiple table positions, fixation with a thermoplastic mask system without bite block and position verification with ExacTrac (Brainlab, Feldkirchen, Germany). In this study a deviation before correction is reported with mean translational 3D vector of 1mm [20]. The size of this deviation shows that repeat position verification and correction are necessary if the fixation system allows small patient movements. However, if a Cone Beam CT is used it is not always possible to verify the patient position after table position changes. The alternative strategy is to further optimize the frameless fixation system using a bite block or vacuum mouthpiece. The positioning accuracy during treatment using this strategy has not yet been fully examined.

II: CLINICAL STUDIES, CHAPTERS 3 AND 4

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 (Brainlab, Feldkirchen, Germany). Local control was defined as first endpoint. We found that radiation dose and Karnofsky Performance Score (KPS) were the two factors associated with local control, despite the fact that larger metastases received lower doses. Metastases treated with 15 Gy or less had a 12-month local control rate of only 37%, which can be considered insufficient.

From this we concluded that a higher Biological Equivalent Dose (BED) would be needed for the large metastases (PTV > 13 cm³). A higher single fraction dose was considered not safe, based on RTOG 90–05 [21]. In 2006–2007 publications appeared with encouraging results of FSRT of large brain metastases [22,23]. Therefore we decided that fractionated SRT (FSRT) would be indicated to improve local control of large brain metastases. The rationale was that fractionation would enable us to treat the tumor with a higher $\text{BED}_{12}$, while protecting the normal brain due to a lower $\text{BED}_{2}$. We decided to use the 3x8 Gy scheme, because the BED model suggested this prescription would be safe and could possibly improve local control. At the same time we decided to do a systematic literature review to assess 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 260 papers a relation between dose and local control could be derived. The conclusion from this review was in line with our own results in chapter 3a, i.e. an excellent 12-month local control rate with a single fraction dose of 20 Gy or more and a disappointing local control rate after administering a single fraction dose of 15 Gy.

In chapter 3c the results of FSRT are reported in a second cohort of patients treated from September 2007 through September 2009. This cohort only contained patients who received FSRT for one of the following two reasons: PTV size > 13 cm³ 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. With all known shortcomings of a retrospective comparison and the small patient numbers the conclusion was that the fractionated scheme of 3x8 Gy was not clearly superior to 15 Gy single fraction. This result may be cautiously interpreted as in agreement with the results of the literature review of chapter 3b. For FSRT with three fractions a dose per fraction of at least 8.5 Gy would be needed for sufficient local control.

Chapter 4 deals with lesion growth after SRT of brain metastases. Chapter 4a deals with radiation induced lesion growth, also called pseudo-progression, after SRT of brain metastases. 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. In chapter 4b we describe 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 progressive lesions and in 30% the cause of the progression could not be determined. The main conclusions were that patients with pseudo-progressive lesions could remain asymptomatic, but that the clinical course of patients with symptomatic pseudo-progression was similar to the clinical course of patients with tumor progression. In other words, symptomatic pseudo-progression is serious radiation toxicity.

The clinical studies in chapter 3 and 4 are about SRT of brain metastases and mainly deal with the relation between dose and local tumor control and with the late toxicity of SRT. Some important aspects of these studies will be discussed further.

**LOCAL CONTROL**

We used local control, defined as the absence of progression of the irradiated tumor, as an endpoint to evaluate the effect of SRT of brain metastases. There is evidence indicating that local control is beneficial in contrast to progression. The latter can be associated with neurological signs or symptoms. In a Japanese trial local control of the irradiated brain metastasis was found to be the most important factor for stabilizing neurocognitive function [24]. The conclusion of an American single center study about SRT of brain metastases is that most local recurrences are symptomatic and associated with neurologic deficits [25].

Local control is not a common endpoint used to evaluate the efficacy of oncological treatments. More common endpoints are response rate, progression free survival, overall survival or indicators of quality of life, but these endpoints are not always suitable for the evaluation of the efficacy of brain metastases treatments. Recently the challenges relating to the evaluation of response and clinical benefit in this field were extensively reviewed [26]. Response assessment criteria for brain metastases have been proposed by an international working group of experts [27]. However, this group acknowledged that progression after SRT could not be diagnosed based on volumetric criteria alone. The main difficulty in SRT of brain metastases is that treatment effect cannot be evaluated by lesion measurement alone, because lesion growth does not equal tumor progression. If lesion growth is based on pseudo-progression there is radiation induced normal tissue damage, which probably coincides with regression of the tumor. However, there is no consensus about diagnostic criteria to distinguish tumor progression from pseudo-progression. Not all authors report tumor progression, pseudo-progression...
and/or radiation necrosis in the same way [28]. The interpretation of lesion growth after SRT is difficult, there is considerable interobserver variability and a diagnosis is often impossible without additional imaging [29].

However, from the patient's point of view, clinical benefit is the most important result of a treatment. A treatment resulting in an enlarging lesion cannot be regarded as successful, whatever the cause of this enlargement. Symptomatic tumor progression and pseudo-progression are clinically similar, as was reported in chapter 4b. Therefore, local control, defined as absence of enlargement of the treated lesion on the latest imaging compared to the previous imaging, can still be regarded as the (surrogate) endpoint of choice representing clinical benefit. However, local control and progression are not reliable endpoints to evaluate the anti-tumor effect of (new) treatments. Consensus about diagnostic criteria for the growing lesion after SRT is needed before anti-tumor treatments can be evaluated more reliably.

**DOSE**

As was pointed out in chapter 3a the treatment results of a single fraction of at least 20Gy of small brain metastases generally are sufficient. For metastases with a diameter larger than 3cm FSRT is needed to be able to safely deliver a sufficiently high biological effective dose. Radiobiological models would be useful to convert a high single fraction dose to a biologically equivalent dose scheme for fractionated treatment. Most radiobiologists agree that the LQ model can reliably predict biologically equivalent schemes with low doses per fraction, but should not be applied to doses per fraction from 18 Gy and higher [30,31]. Alternative models have been developed in order to improve prediction of the biological effect of higher doses per fraction. In chapter 3b we used the LQC model proposed by Joiner [32]. However, improvement of FSRT cannot be achieved with theoretical models alone. Clinical results are necessary to measure the effect of a treatment scheme.

In chapter 3b clinical results of some FSRT schemes were described. Recently more results with different dose schemes have been published, but prescribed doses varied considerably, sometimes within a center [33-36]. Up till now no new reliable clinical results are available that would change the conclusions of our review described in chapter 3b.

**TOXICITY**

In chapter 4a we showed that pseudo-progression probably is a radiation effect on the normal brain tissue surrounding the brain metastasis. In chapter 4b we report that pseudo-progression can cause irreversible neurologic symptoms. Evidently, it is important to find ways to avoid this toxicity.

Pseudo-progression probably is a manifestation of radiation necrosis of the brain. The relation between dose, volume and radiation necrosis rate has been thoroughly investigated and published in 2010 in the "Quantec" paper [28]. An important statement in this paper is: “The large variation in absolute complication rates among studies is difficult to comprehend, but it might relate to differences in the definitions of the volume and toxicity, the avoidance of critical structures, and the type and length of clinical follow-up.” Despite these open questions, many authors agree on a relation between the V12 (volume receiving ≥ 12Gy) and the risk of necrosis [28,37-39]. A V12 larger than 5-10 cm³ would predict a higher risk on necrosis. Strikingly, not all authors use the same definition of this V12: some define the V12 as the volume of normal (brain) tissue without tumor and others as the volume of any tissue including tumor that receives ≥ 12Gy (personal communications with Blonigen and Minniti). Moreover, there is no accepted definition of the V12 in cases with multiple brain metastases and a recalculation is needed for patients receiving FSRT. Despite this variety of definitions
there is enough evidence for a direct relation between the volume of irradiated brain tissue and the risk of radiation necrosis of the brain. Therefore, a strategy to reduce the high dose volume in the brain is needed.

In radiation oncology the margin concept has been widely accepted. The aim of CTV-PTV margins is to give 90% of patients at least 98% EUD (equivalent uniform dose) in order to achieve an optimal TCP (tumor control probability) [40]. The margin concept has in fact been developed to improve curative radiotherapy, to be certain that all tumor cells receive the prescribed dose. However, for the majority of patients the goal of SRT of brain metastases is palliation. Complete response rates are low and a partial response is already considered a treatment success. If a partial response is the goal, we could reconsider the use of the CTV-PTV margin that is used in order to achieve a complete response. The use of this CTV-PTV margin, that might not be necessary to achieve a partial response, might in fact cause harm to the patient. The CTV-PTV margin contains mostly normal brain tissue, the amount of which increases considerably with increasing CTV volume, as simple mathematics proves. A larger PTV will inevitably lead to a larger V12 and hence to a higher necrosis risk.

There is evidence that smaller or no CTV-PTV margins are to be preferred. In 2008 a retrospective comparison was published of linac SRT in 93 single brain metastases with or without a 2mm GTV-PTV margin [41]. Local control was not better in the patients treated with a margin, but the rates of grade 4 complications (prolonged treatment with steroids necessary) were 19.6% and 7.1% in patients treated with or without margins, respectively (p=0.02). In 2014 a randomized phase III trial was published, comparing 1 mm and 3 mm GTV-PTV margin in 49 patients with 80 brain metastases [42]. Local control rates did not differ between both groups. Radiation necrosis was diagnosed in 5 patients in the 3 mm group and 1 patient in the 1mm group, but, although striking, this difference was not statistically significant. Gamma-knife departments almost invariably treat brain metastases without margin. Although we are not aware of a clinical study comparing results of linac and Gamma Knife SRT, published local control rates of Gamma-knife series do not appear to be worse.

The size of the CTV-PTV margin is certainly not the only factor responsible for the development of radiation necrosis. In a large series of patients treated on the Gamma Knife without CTV-PTV margins adverse radiation effects are reported in 5.4% of the treated metastases [43]. The 1-year probability of radiation toxicity was higher after treatment of larger lesions. Even without the use of margins more normal tissue is irradiated if the PTV is larger. In 2004 a report was published of a study that retrospectively examined patients who had lived longer than two years after Gamma-Knife SRT (without GTV-PTV margin) [44]. Of the 22 patients who had survived for more than 2 years, 14 had radiologic signs of radiation necrosis. The paper did not mention the rate of symptomatic necrosis.

In conclusion there are convincing reasons to reconsider the use of CTV-PTV margins in palliative linac based SRT of brain metastases.

Important side effects of cranial SRT besides necrosis of the brain have not been documented. The reported serious radiation toxicity after whole brain irradiation, such as neurocognitive impairment and even dementia in long-term survivors, probably does not occur after SRT alone, because of the low brain dose levels [24,45,46]. Nevertheless, it is important to know the effects of SRT on quality of life and neurocognitive function and therefore, this is presently the subject of research in our hospital.
INDICATIONS FOR SRT OF BRAIN METASTASES
Classically SRT is indicated in patients with 1-4 brain metastases, the largest of which has a diameter not more than 4cm, who have a Karnofsky performance score of at least 70 and who do not have extracranial tumor progression (unless with realistic options for systemic treatment). A number of prognostic scores have been developed to select patients who might benefit from SRT [47,48]. Adding whole brain irradiation (WBI) to SRT is not indicated[49]. Recently results from a large observational study were published that suggested that SRT might be an alternative for WBI in selected patients with five to ten brain metastases [8]. However, this indication for SRT is not yet generally accepted.

A recently published EORTC study showed that WBI after complete resection of a brain metastasis does not prolong functional independence and overall survival [50]. Since the publication of these results most centers do not advice the use of adjuvant WBI anymore after a complete resection. However, the two-year relapse rate at the initial site after surgery alone of 59% in this study was still high. Therefore, some centers started to give postoperative SRT to the resection cavity after incomplete but also after complete resection in order to decrease local relapse rates. Up till now only papers reporting single center experience with postoperative SRT have been published [51-53]. Reported results in these publications are promising, although the risk of leptomeningeal metastases is a matter of concern [54].

FUTURE PERSPECTIVES

OPTIMIZING TREATMENT

CTV-PTV MARGINS
In chapter 4b we reported that at least 19 out of 237 treated patients experienced neurologic deficits probably caused by radiation toxicity of the surrounding normal brain. As has been discussed, the high radiation doses received by the normal brain tissue within the CTV-PTV margin might be responsible for much of this toxicity. However, a CTV-PTV margin might not be necessary at all if a complete remission of the irradiated tumor is not the aim of the treatment. Therefore, our new department’s protocol of SRT of brain metastases will include CTV-PTV margins of 0 mm.

DOSE PRESCRIPTION AND REPORTING
A second question that needs to be addressed in the future concerns the optimal practice of dose prescription in linac SRT. In many linac centers the SRT dose is prescribed to an isodose covering the PTV. Historically the 80% isodose is frequently used as specification isodose, thus taking advantage of areas within the target receiving higher doses than the prescribed dose. However, there are theoretical arguments in favor of a different practice of dose specification. The historically used inhomogeneity within the target, when specifying on the 80% isodose, might not be optimal. After a theoretical exercise in our department we concluded that prescribing the SRT dose on the 60% isodose would result in a better trade-off between dose in PTV and dose in normal tissue (unpublished results). However, dose specification on the 60% isodose might not be safe if a CTV-PTV margin is used and the PTV contains normal brain tissue.

Currently the practice of dose prescription varies considerably between centers practicing SRT in the Netherlands. Therefore, an initiative aiming at uniform dose prescription and reporting in the Netherlands was started in the LPRNO (Assembly of Dutch Radiation Oncologists working in Neuro-Oncology).
FRACTIONATION
As has been discussed, fractionation is needed if SRT is applied to large target volumes. FSRT is probably safer than single fraction SRT, because lower doses per fraction are applied to surrounding normal tissues. A second possible advantage is that re-oxygenation between fractions can take place in tumor cells, making the cells more radiosensitive and the treatment more effective. However, the radiobiology of the relatively high doses per fraction that are used for SRT is not completely understood. More fractionation schemes will have to be tested in clinical practice to optimize the treatment.

OUTCOME

MORE PATIENTS WITH BRAIN METASTASES WILL BE ELIGIBLE FOR SRT
Patients with specific types of cancer responding to new targeted therapies, such as Her2+ breast cancers and EGFR mutated or ALK rearranged non small-cell lung cancers, may live considerably longer thanks to these new drugs, but are often more prone to developing brain metastases [55,56]. Research is directed at developing drugs that cross the blood-brain barrier. However, up till now in most of these patients the response duration of the brain metastases is too short to be able to avoid cranial radiotherapy [57,58]. These patients with brain metastases as the only site of tumor activity and long lasting systemic disease control heavily rely on radiotherapy for their quality of life. SRT is the preferred treatment for their brain metastases to retain this quality of life. In the near future more targeted drugs are expected and, therefore, more long surviving patients with metastases in the brain only are expected to need SRT. For these growing numbers of patients regular follow-up after SRT will be important in order to detect and treat new brain metastases before they cause neurologic deficits.

Furthermore, patients with five to ten small brain metastases might be better off with SRT than with WBI. Presently a Dutch randomized phase III study is in preparation to address the question what treatment is optimal for this category of patients. Another new indication for SRT in patients with brain metastases is postoperative SRT of the resection cavity. The value of SRT in the postoperative setting is the subject of ongoing research.

THE RADIATION-ONCOLOGIST SHOULD BE MORE INVOLVED IN THE FOLLOW-UP AFTER SRT OF BRAIN METASTASES.
Most patients with brain metastases have a poor prognosis. Follow-up after SRT should be restricted only to those patients who might possibly benefit from repeated hospital visits and imaging. Follow-up should not be proposed to patients in poor general condition who are likely to die within some months.

For almost all patients the brain is their most precious organ that contains all aspects of their personality. The fear that new metastases might invade the brain or that the treated tumor(s) might continue to grow can be reason enough for patients to consent to follow-up imaging. Confirmation that there is no tumor activity in the brain can reassure the patient that his or her personality and cognition are likely to remain intact. Although reassurance of the patient is a good reason to do post-SRT follow-up, the most important reason for follow-up is that imaging may enable early detection of new brain metastases. New brain metastases should ideally be treated before they cause neurologic deficits. With regular, preferably at least three-monthly, follow-up imaging new metastases or local recurrences can be detected and treated in an early stage [59]. Moreover, WBI with its unwanted side effects might be avoided, if the number and total volume of newly detected brain metastases allow the use of SRT [59].
This three-monthly follow-up imaging will routinely consist of an MRI scan, preferably with a perfusion series, in order to detect recurrent tumor growth at the irradiated site or new brain metastases. If post-SRT lesion growth is detected, the perfusion scan may be helpful to make the distinction between tumor progression and pseudo-progression. No additional hospital visit is needed for the patient with post-SRT lesion growth if the perfusion scan is already included in the routine follow-up imaging protocol. Radionuclide imaging techniques can be applied additionally to determine the cause of post-SRT lesion growth as seen on follow-up MRI, but they are not suitable for incorporation into routine follow-up [60]. However, as was reported in chapter 4b, even with perfusion MRI the cause of post-SRT lesion growth may remain uncertain. PET scans using the amino acid tracer F-DOPA have recently been reported to perform better than perfusion MRI in differentiating tumor progression from pseudo-progression [61]. Therefore, PET scans using amino acid tracers will probably become a more important diagnostic tool for patients with post-SRT lesion growth.

Here the question arises how to organize post SRT follow-up of patients with brain metastases. In our view, the responsible person for this follow-up should be a member of the multidisciplinary (neuro) oncologic team. Furthermore, this person preferably should have knowledge about and experience with the questions that arise after SRT and have insight into the additional treatments that may have to be applied. Our results showed that the growing lesion after SRT is not a rare situation in the practice of a dedicated radiation oncologist. Referring specialists who are not involved in SRT do not encounter these difficult lesions regularly and may tend to regard a growing lesion as tumor recurrence. In fact some patients who were not followed in our hospital and who had evident pseudo-progression were referred to us for re-irradiation with the incorrect diagnosis of tumor progression. Therefore, we are convinced that involvement of the radiation oncologist in post-SRT follow-up is a prerequisite. Improvement of outcome is only possible if the treating physician can see and study all treatment effects.

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. Large brain metastases need a sufficiently high biological equivalent dose in order to obtain adequate tumor control rates. Fractionated SRT is needed for safe administration of such higher biological equivalent doses. Lesion growth after SRT can be caused by radiation toxicity of normal brain tissue. This pseudo-progression can be symptomatic or asymptomatic. Spontaneous clinical improvement of symptomatic pseudo-progression is exceptional.
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Discussion and future perspectives


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