Stereotactic radiotherapy of intracranial tumors

Optimizing treatment and improving outcome

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CHAPTER 1

Introduction

INTRODUCTION

A stereotactic treatment can be defined as a treatment in which a three dimensional coordinate system is used to very precisely localize a point inside the body of a patient. Stereotactic radiotherapy and radiosurgery are widely used treatment modalities that originated from stereotactic surgery in the 1950's and 1960's.
Nowadays radiosurgery and stereotactic radiotherapy have many common characteristics. However it is interesting to realize that both treatment modalities had a very different history. Neurosurgeons started to use ionizing radiation for highly selective destruction of small amounts of tissue in the brain. In later years they developed radiosurgery into the present treatment that incorporates image guidance and even fractionation. Radiation Oncologists started with a very different background. They used ionizing radiation for tumour treatment using the biologic principles of fractionation. In a later stage they incorporated stereotactic guidance and the specific biologic properties of high fraction doses into the current stereotactic radiotherapy.

The different development routes of both disciplines are described in the first two paragraphs. In the third paragraph the contemporary practice of cranial stereotactic radiotherapy is described.

1. DEVELOPMENT OF RADIOSURGERY IN NEUROSURGERY

The idea of stereotactic localization arose in London early in the twentieth century. Horseley and Clarke developed a stereotactic instrument with the aim to localize intracranial structures in the monkey brain. This would enable them to selectively destruct predefined structures in the monkey brain for neurophysiologic research [1-3]. The first stereotactic frame for human use was developed in Philadelphia in the 1940s [1]. This is a rigid reference frame fixed to the head of the patient and used to relate a target inside the body to a point in space with known x, y and z coordinates. Spiegel and colleagues used this frame to make selective lesions in the human brain for psychosurgery and for the treatment of movement disorders. The less invasive character and decreased operative mortality rate of stereotactic procedures was considered their great advantage [2].
Lars Leksell in Stockholm first explored the use of radiation in combination with the stereotactic method [3].
He developed the idea of radiosurgery to be able to produce lesions in the brain using a method that was even less invasive than stereotactic surgery [4]. In 1951 Leksell coupled an orthovoltage X-ray tube to his stereotactic frame to treat trigeminal neuralgia [5]. However, it was not possible to make small localized lesions in the brain using orthovoltage X-rays. Other radiation modalities were needed to enable more conformal treatments. In the late 1950s the group of physicists in Uppsala started to develop a system that used a cyclotron to produce proton beams for treatment purposes [6]. Proton treatment seemed an ideal modality to produce localized lesions and therefore, a technique for using protons in stereotactic treatments was developed [7]. Leksells group performed the first stereotactic proton treatments in Uppsala in 1960. Results of stereotactic proton treatments of pituitary tumours and arteriovenous malformations (AVM's) were reported by a group of neurosurgeons in Boston [8,9]. The purpose of these proton treatments was the destruction of small regions of tissue in the brain in a single session and were therefore designated as stereotactic radiosurgery (SRS) and performed by neurosurgeons. Stereotactic proton treatments, however, were considered impractical and a more easy-to-use radiation modality was sought.
As a better solution for radiosurgery two possible alternatives were considered, namely a machine based on Cobalt60 sources and a linear accelerator. Although a linear accelerator adapted for the purpose seemed the most attractive alternative, the Cobalt60 machine was

at that time the more realistic solution. The first Gamma knife was developed as a machine containing 179 Cobalt sources. The great advantage of the apparatus was that the staff of the neurosurgical clinic could handle it, with the physicist responsible for the regular calibration of the dose rate, the radiation safety of patients and personnel and, together with the surgeon, for the treatment plan [10]. The device was initially mainly intended for use during functional neurosurgery. The first Gamma Unit was installed in the Sophiahemmet Hospital in Stockholm in 1968 and the second unit was installed in the Karolinska Hospital in 1974[4]. Target definition was performed using plain radiography and air encephalography; angiography was used for the treatment of AVM's.
The introduction of the CT scan enabled better target definition and CT was incorporated into the practice of stereotactic radiosurgery [11]. The Karolinska group described in 1976 how the stereotactic coordinates of the target could be accurately transferred from the CT scan to the treatment machine [11]. At this point in time it became possible to treat intracranial tumours with photon radiosurgery. Vestibular schwannomas and craniopharyngiomas were the first tumours treated with radiosurgery, later followed by pituitary adenomas, meningiomas and pineal tumours [4]. From the 1980's frameless methods were developed as well for intracranial operative guidance [12,13]. Neurosurgeons considered and still consider radiosurgery as a surgical technique for non-invasive destruction of intracranial tissues or lesions that may be inaccessible or unsuitable for open surgery [4]. The precision of radiosurgery made it possible to spare normal tissue and deliver a high radiation dose to tumour tissue only. Radiosurgery has developed into a neurosurgical subspecialty. In the 1980's however, the first reports appeared of stereotactic treatments on adapted linear accelerators by collaborating Neurosurgery and Radiation-Oncology groups [17-19]. From now on it was also possible to use a high number of precisely collimated linac beams to deliver a high radiation dose with a steep dose fall-off. However, many neurosurgeons considered the advantage of the relatively simple and reliable technology of the gamma units more important than the disadvantage of the regular source replacements and the gamma units remain in use in many centres despite the availability of linacs for radiosurgery.

2. DEVELOPMENT OF STEREOTACTIC TREATMENTS IN RADIOTHERAPY

Radiation as an anticancer therapy became possible by two scientific breakthroughs in physics late in the 19th century. Wilhelm Röntgen discovered X-rays in Germany in 1895 and a few months later Henri Becquerel discovered natural radioactivity in France. In the first half of the twentieth century X-ray therapy was possible with machines that produced low energy X-rays (10-50kV). These machines were only suitable to treat superficial tumours. Later orthovoltage X-ray machines (200-500kV) became available for the treatment of deep-seated tumours [14]. Drawbacks of these two treatment modalities were the high skin doses and the considerable tissue attenuation, especially in bone. Radium became available as a source of high-energy photons and was used for brachytherapy and later for tele-radium therapy [15,16]. At first radiation was used for treatment of non-malignant conditions as pain and chronic inflammation, later radiation was also used to treat malignant tumours. Until 1920 the German school dominated in radiation therapy with an approach characterized by the use of a few "caustic" doses of radiation [14]. Within a few years normal tissue complications were seen that could be ascribed to these treatments. After this period French research became influential. An important development was the work of Regaud in 1922 in Paris that led to insight into the value of fractionation [17]. In the 1930's consensus was reached in the radiotherapy community in favour of fractionated treatment. With fractionation a high dose could be given that was able to cause sufficient cell kill in tumour tissue, while normal tissue could recover between fractions. With almost all radiotherapy techniques a considerable radiation dose was delivered to normal tissues adjacent to tumour and only by fractionation these normal tissues could be spared. With fractionated schemes orthovoltage radiotherapy

alone already could produce reasonable five-year survival rates in the 1930's in tumours that would have been practically incurable before [18]. Megavoltage external beam radiotherapy began with the first 1MV unit in London in 1937 and the first linear accelerator also in London in 1948 [20,25,26]. Since then there has been an enormous development in the technology of linacs. In the 1950's telecobalt units came into use for megavoltage teletherapy as well [19]. Their advantage was their relatively simple and reliable technology, but their disadvantage was the necessity of regular source replacements. In the radiotherapy world this disadvantage was considered more important than the mentioned advantage and this led to the gradual disappearance of cobalt units in the western world, where more and more linacs became available. In the 1980's radiosurgery techniques were developed on conventional linear accelerators [20]. Patients were positioned and immobilized using stereotactic techniques and arc therapies with circular collimators were developed [21]. Systems with separate gantry and couch movements during treatment were also introduced [22]. In some linac radiosurgery systems the head was supported on a floor stand independent from the treatment table [23]. The separate floor stand was introduced for stability and accuracy, but later abandoned for safety reasons. Linac Radiosurgery was in that period mostly performed by collaborating Neurosurgery and Radiation Oncology groups.
Since then linac radiotherapy has seen a great evolution. Important developments in relation to stereotactic radiotherapy (SRT) were:

- *Treatment planning*
  Advances in treatment planning in radiation oncology were largely based on the enormous advances in computer technology. The introduction of the CT scan enabled more accurate calculation of dose distributions. Although radiotherapy has always been image guided, the introduction of the CT and MRI scanning enabled better tumour imaging and consequently enabled more conformal treatment plans [14].

- *The margin concept*
  The concept of GTV (gross tumour volume), CTV (clinical target volume) and PTV (planning target volume) is widely adopted in the radiation oncology community. For all treatments a margin between CTV and PTV is used to account for treatment uncertainties and inaccuracies [24,25]. To calculate the CTV-PTV margin a margin recipe is used that takes into account all uncertainties and inaccuracies of the preparation and execution of the treatment. The aim of the CTV-PTV margin is to give 90% of the treated patients 98% EUD (equivalent uniform dose). The idea behind this margin concept is that all cells of the malignant tumour should receive the prescribed dose and that no tumour cells should be in the area of dose fall-off. Examples of the factors used to calculate margins are the pixel size of the planning CT, the dimensions of the laser beams crossing in the isocenter, accuracy of image registration, the intrafraction movement of the patient and the accuracy of the patient set-up. If these principles are used, CTV-PTV margins will never be 0mm, even in stereotactic radiotherapy.

- *Image guidance*
  With image guidance the application of tighter margins and higher dose gradients became possible [26,27]. Imaging systems integrated with the treatment machine enable imaging of the target just before treatment and consequently online correction of setup errors can be performed. Reduction of setup errors allows reduced CTV-PTV margins and, by doing so, a reduction of the volume of irradiated normal tissue, necessary for stereotactic treatment. Evidently, setup based on image guidance is essentially different from setup based on stereotactic coordinates.

- *Multi-leaf collimators*
  In the 1980's multi-leaf collimators (MLC) were developed for linear accelerators, initially for automatic beam shaping, but soon MLC's were also used for shaping of non-uniform dose distributions [28,29]. The advent of Intensity Modulated Radiotherapy (IMRT) enabled more conformal dose distributions and "dose painting", planned inhomogeneous dose distributions to give higher doses to designated parts of the target volume [30]. For conventional radiotherapy 10mm leafs were developed, but for stereotactic treatments MLC's with smaller leaf-widths (5mm and 3mm) became available. MLC's with 3mm or 5mm leaves were found to provide better dose conformity and better sparing of organs at risk [31]. These narrow-leave MLC's enabled the combination of IMRT and stereotactic radiotherapy.

- *Dedicated Linacs*
  Linear accelerators specifically designed or adapted for stereotactic radiotherapy were developed.
  - Conventional linacs have been adapted to meet stringent requirements for stereotactic radiotherapy, especially with respect to mechanical stability of gantry and treatment couch. No consensus has been reached about exact accuracy criteria for dedicated linacs. The isocentric accuracy is checked on a regular basis [23]. It has to be within 0.4mm to be comparable with the Gamma-Knife's values [32]. The Novalis system (Brainlab AG Feldkirchen, Germany) is a dedicated linac with a microMLC combined with two orthogonal X-ray tubes for online set-up correction.
  - The Cyberknife system is different from a conventional linac and consists of a small linac fixed to a robotic arm, combined with orthogonal X-ray tubes for online set-up correction. This system was developed by Accuray Inc in Sunnyvale (Ca, USA) as an instrument for performing non-invasive stereotactic radiosurgery. The first clinical experiences were published by neurosurgeons and radiation oncologists from Stanford [33]. The accuracy of treatment delivery of this system is reported as less than 1mm with very thin CT slices [34].
  - The Tomotherapy H series and its predecessor HI-ART II (Accuray Inc Sunnyvale, Ca, USA) are radiation treatment systems originally designed for image guided IMRT. This system is characterized by integration on a single platform of intensity modulated radiotherapy, onboard CT imaging for daily target localization with the patient in the treatment position, and adaptive planning tools [35]. The accuracy for localizing dose to a small target is within 2 to 2.4 mm for SRS treatments using image-guided IMRT [35].

As a consequence of these developments more and more radiotherapy centres were able to offer stereotactic radiotherapy to their patients. The different techniques and biologic principles however have led to a different practice of stereotactic radiotherapy in the hands of radiation oncologists compared to neurosurgeons.

3. CONTEMPORARY STEREOTACTIC RADIOTHERAPY

In the 21st century the technology to perform radiosurgery or stereotactic radiotherapy has become widely available. High-end linear accelerators can meet the stringent requirements for stereotactic radiotherapy. In many radiotherapy departments high dose high precision treatments of intracranial lesions are performed and classified as stereotactic radiotherapy. Many neurosurgeons perform radiosurgery, which can be regarded as a similar high dose high precision treatment. Consequently there are a variety of treatment techniques and responsibilities in the field of stereotactic treatments. The current practice of stereotactic radiotherapy and radiosurgery is summarized in this chapter.

DEFINITIONS AND RESPONSIBILITIES

Stereotactic Radiosurgery has been defined by the American Society of Radiation Oncology (ASTRO) as radiation delivered via stereotactic guidance with approximately 1mm targeting accuracy to intracranial targets in 1 to 5 fractions [36]. Although Stereotactic Body Radiation Therapy (SBRT) has been defined by ASTRO, there is no such a consensus definition of cranial Stereotactic Radiotherapy (SRT) [37]. It seems logical to adopt a comparable definition for cranial SRT, but without the limitation of the maximum number of 5 fractions. In many Radiation Oncology Centres cranial SRT is used either as single fraction or as multiple fraction treatment via stereotactic guidance or image guidance. We define cranial SRT as an external beam method to very precisely deliver a radiation dose in either a single fraction or in multiple fractions to an intracranial target via stereotactic guidance or image guidance. We regard SRS equivalent to single fraction SRT.

In the Neurosurgery community there are somewhat different views on the definition of Radiosurgery. Adler et al define Radiosurgery as a procedure that involves the active participation of a surgeon and in which spatially accurate and highly conformal doses of radiation are targeted at well-defined structures with an ablative intent [38]. Whereas ASTRO describes a multidisciplinary team as a requirement for a quality SRS program, for Adler et al the neurosurgeon is leading [37,38].

Currently cranial stereotactic radiotherapy is widely used in many radiotherapy centres and neurosurgical centres. Developments in both disciplines have influenced the used techniques. At present a variety of techniques is designated as SRT or SRS.
Discussion still exists what medical specialty should be leading in the performance of stereotactic radiotherapy.
There is no international consensus about the question who should be responsible. In some centres neurosurgeons are responsible for the indication for the treatment, for target definition, dose prescription and planning, in other centres radiation oncologists are responsible, whereas many centres have mixed solutions with shared responsibilities. Consequently reimbursement issues have been raised in the US [39].

Many neurosurgeons consider radiosurgery a form of surgery. They describe a series of highly focused radiation beams as a non-invasive surgical knife that is used to ablate small amounts of tissue [40]. In their view radiotherapy is different from radiosurgery, because radiotherapy is based on different radiobiological principles. Adler et al state that radiotherapy was historically less concerned with targeting accuracy and anatomic precision, because fractionating was the way to protect normal tissues. Many Radiation Oncologists however, consider all treatments with radiation beams, including beams under stereotactic guidance, as radiotherapy, irrespective of the radiobiological background or the amount of precision of the treatment.

INDICATIONS FOR CRANIAL STEREOTACTIC RADIOTHERAPY AND RADIOSURGERY

Historically the first indications for radiosurgery concerned functional treatments [5]. Trigeminal neuralgia is still an indication for radiosurgery in many centres and neurosurgeons are usually responsible for the indication and the treatment. The treatment of AVM's and epilepsy are accepted indications for radiosurgery as well and in most centres where these treatments are performed neurosurgeons are leading in the treatment process. Most stereotactic treatments, however, are of patients with benign and malignant tumours and in this field the radiation oncologist's role has become more important [36]. Presently brain metastases, vestibular schwannomas, meningiomas and AVM's are the most common indications for stereotactic treatments [41]. There is discussion about the question if radiosurgery is beneficial for patients with more than four brain metastases. In a report of a large prospective

observational study the authors conclude that stereotactic radiosurgery in patients with five to ten brain metastases is non-inferior (with respect to survival and adverse events) to that in patients with two to four brain metastases [42]. However, many radiation-oncologists still advise whole brain radiotherapy to patients with more than four brain metastases.

TARGET DEFINITION AND MARGINS

The basis of all high precision treatments is accurate target definition. Most target volumes are delineated on MRI images, with some exceptions, such as AVM's, where angiography is needed.
A source of inaccuracies in target definition that has long been disregarded is contouring variability between observers [43]. Contouring variability can even have dosimetric consequences [44].
Distortions in MRI scans are corrected to avoid inaccuracies in target definition [45].
As most radiotherapy planning systems use CT scans to compute a treatment plan, MR-CT registration is necessary. Inaccuracies can occur in the registration process and have to be taken into account [46,47].
For accurate treatment planning of small structures CT slice thickness is important and should preferably not be more than 2mm [48].

In modern stereotactic radiotherapy there is no consensus about the question if CTV-PTV margins should be used.
Radiation oncologists generally do use CTV-PTV margins to correct for uncertainties and inaccuracies of the preparation and execution of external beam radiotherapy [25,49]. This margin concept is based on convincing theoretical considerations, but no formal clinical trials have beam performed to show its validity.
Although the margin concept has been designed for fractionated radiotherapy, it is applied to single fraction treatments as well. Consequently the high fraction dose that is prescribed in a stereotactic treatment is also applied to the normal tissue within the CTV-PTV margin. The trade-off between possible gain in local control and increase in normal tissue damage is unknown. In one study in patients with brain metastases the application of a 1mm CTV-PTV margin led to improved local control without increased toxicity, compared to historical controls treated with no margin [50]. In a randomized trial comparing a 1mm with a 3mm CTV-PTV margin local control rates did not differ between both groups [51]. Radiation necrosis was diagnosed in 5 patients in the 3mm group and 1 patient in the 1mm group, but, although striking, this difference was not statistically significant. In another study a non-randomized comparison was done between 2mm and 0mm margin in patients with brain metastases. In this study no difference in local control was found, but an increased late toxicity rate for 2mm margin [52].
Radiosurgeons have traditionally trusted the accuracy of the stereotactic system, without considering corrections of possible inaccuracies. The idea is that the target is accurately defined and that the prescribed single fraction dose is high enough to sterilize tumour cells in the immediate vicinity of the GTV. Another consideration for omitting margins is the fact that the large dose inhomogeneities that have to be accepted within the target would be unacceptable in the normal tissue within the margin.
Therefore, followers of the neurosurgical tradition generally do not apply GTV-PTV margins. This practice seems to be independent of the treatment machine used, as not only neurosurgeons using the Gammaknife but also neurosurgeons performing Linac radiosurgery do not report application of margins around the GTV [53-55].
Different opinions with respect to the use of margins result in differences in the given treatment. The same dose prescribed to the isodose line covering the GTV or the GTV+ 2mm the results in very different maximum and mean doses in the GTV. These differences are particularly important if treatment results are compared.

DOSE PRESCRIPTION AND FRACTIONATION

Dose prescription for radiosurgery/stereotactic radiotherapy traditionally does not follow the international guidelines for conventional external beam radiotherapy [49]. Until recently the ICRU Report 50 guideline was dose prescription to a representative point in the target with the requirement that the dose in the target would be between 95% and 107% of the prescribed dose. With most SRT techniques this dose homogeneity was not possible, but also considered unimportant with almost no normal tissue inside the target. Doses for stereotactic treatments are usually prescribed to the isodose line covering the target or to the (near) minimum dose in the target. An additional advantage of this practice is a sharper dose falloff outside the target. However, the disadvantage is that the EUD of a prescribed dose highly depends on the prescription isodose. Consequently the effect of a certain dose is difficult to establish if dose prescription and thereby the EUD varies between patients.

High doses per fraction are a common characteristic of stereotactic treatments. Radiobiologists have for many years devoted much attention to the effects of fractionated treatments using lower doses per fraction. Radiobiological models were derived for the comparison and quantification of the effectiveness of different radiation regimes. Of these the LQ model is the most commonly used [56]. However, most of the data used to generate this model are obtained in vitro at doses well below those used in radiosurgery. There is an on-going discussion about the question whether the LQ model is appropriate to model high dose per fraction effects in radiosurgery. Proponents of the applicability of the LQ model state that it would be reasonable to use it up to about 18 Gy per fraction [57,58]. Opponents argue that clinical results have shown that tumour control probability at radiosurgical doses of 15-20 Gy is higher than expected based on the LQ model [59]. The cause of this discrepancy would lie in additional biological mechanisms at higher dose per fraction such as radiation effects on blood vessels that would have impact on radioresistant subpopulations of tumour cells. A threshold dose for these effects is presumed.

TREATMENT PLANNING

Modern stereotactic radiotherapy includes a variety of treatment techniques performed on the available hardware platforms. Most treatment planning software is specific for a certain treatment machine.

Leksell Gammaplan is the planning system for the Gamma Knife (Elekta AB, Stockholm, Sweden).
The Multiplan system is designed specifically for the Cyberknife (Accuray Inc Sunnyvale, Ca, USA).
The TomoTherapy Treatment Planning Software is specific for the TomoTherapy System (Accuray Inc Sunnyvale, Ca, USA).
Novalis is an integrated system for stereotactic radiotherapy with iPlan RT as planning software (Brainlab AG Feldkirchen, Germany).

Linac Stereotactic Radiotherapy can be performed with treatment planning software that is not specifically designed for a certain treatment machine. Internationally accepted standards for the accuracy of an SRT planning system are lacking. Multiple techniques are available for linac SRT: static beams using cones or MLC, IMRT and arc techniques with and without intensity modulation. Not one of these techniques has turned out to be superior, but for specific indications one specific technique may have advantages [32,60].

Standard practice is to derive a number of quantitative criteria from the DVH's for evaluation and comparison of the quality of SRT plans. The most commonly used criteria are: target

coverage, conformity index, homogeneity index and dose in critical structures, some studies also consider the gradient index.

FIXATION AND POSITIONING

Patient fixation for Gamma-knife radiosurgery is classically performed using the Leksell invasive head frame, to which a localization box can be firmly attached. The accuracy of this system is considerable, but small application errors do remain [61]. Over the years more invasive head frames were designed. However, invasive frames have drawbacks. These are patient discomfort and the necessity of having to repeat the invasive procedure if more than one stereotactic treatment is indicated. To avoid these drawbacks so-called non-invasive or relocatable frames were designed. The relocatable frames are necessary for fractionated cranial SRT. Many relocatable frame systems were developed with different methods of fixing the frame to the skull. Anatomical structures that are used in various combinations for fixation are the upper jaw (using a bite block or upper jaw support), the occipital bone, nasion and external auditory canal [62-65]. Whereas users of invasive frames usually consider the positioning accurate due to their tight fixation to the skull, most users of relocatable frames use an additional position verification system to improve positioning accuracy. The positioning of the patient can be verified using stereoscopic kV images, (cone beam) CT scan, EPID, or depth helmet [65].

PARTICLE TREATMENT

Radiosurgery has been performed with protons since the 1960's. The high costs of proton therapy prevented its wide spread use since then. Still some groups advocate proton beam stereotactic radiosurgery (PSRS). They mention the characteristic sharp dose fall-off of proton beams as potential advantage for treating lesions near radiation sensitive structures. This would have to translate into low rates of radiation-induced morbidity. Proton treatments of small intracranial targets can be classified as a form of stereotactic radiotherapy, because they will meet our requirements of stereotactic radiotherapy: "an external beam method to very precisely deliver a radiation dose in either a single fraction or in multiple fractions to an intracranial target via stereotactic guidance or image guidance". The American Society for Therapeutic Radiology and Oncology (ASTRO) considers "proton beam therapy as one of the acceptable forms of external beam radiation therapy that may be used to administer SRS" [66].

Planning studies suggest a benefit of PSRS over Photon SRS, but it is not certain if this advantage would be maintained with today's planning systems [67].
Results of PSRS have been reported in AVM's, acoustic neuromas, meningiomas and pituitary adenomas [68-73]. These results seem to be equivalent to those of photon SRS series, but follow-up duration in most series is not long enough to assess the potential gain of proton therapy with respect to late toxicity [74].Reported techniques vary with different fixation techniques and stereotactic or image-based localization.

FOLLOW-UP

The purpose of follow-up is to monitor treatment results and side effects to be able to treat recurrence or toxicity in an early stage and to be able to improve the treatment for future patients.
In the ASTRO guidelines on radiosurgery follow-up is regarded as essential: "There should be follow-up of all patients treated and maintenance of appropriate records" [36].

Patients who have had SRT for functional disorders are followed clinically and AVM patients are examined by angiography. However, most patients who have had SRT for a benign or

malignant tumor and who are eligible for follow up are examined with MRI scans.
Oncological follow up usually consists of response evaluation by measuring the size of the treated tumor on consecutive images (MRI or other modalities). Criteria have been formulated to be able make an objective distinction between complete response, partial response, stable disease and progression [75-78].
After the high SRT doses per fraction that are administered to metastases, lesion enlargement may be encountered during follow-up that is not based on tumor progression [79]. The pathophysiology of this so-called pseudo-progression is unknown, but it is regarded as a manifestation of radiation toxicity.
In benign tumors a comparable phenomenon is encountered after single fraction or fractionated treatments [80,81]. There are no accepted criteria for the diagnosis radiation toxicity and hence the relation between SRT dose, volume and toxicity risk is not completely known [82].

The risk of radiation-induced cancer certainly deserves attention in patients that receive radiotherapy for benign lesions. It is mainly influenced by the age at treatment and the given dose. Whether fractionation influences radiation induced cancer risk has not been reported. For every 1000 adult cancer patients treated with radiotherapy five excess cancers were estimated by 15 years [83]. In a retrospective cohort study in approximately 5000 patients treated with Gamma Knife radiosurgery no increased risk of malignancy was detected [84]. However second tumors after radiosurgery have been reported [85].

Despite these toxicities, which occur in a minority of treated patients, stereotactic radiotherapy is a non-invasive treatment modality that is of great benefit to many patients with diseases in the brain.

OUTLINE OF THIS THESIS

In 2004 state-of-the-art stereotactic radiotherapy (SRT) started in RCWEST. The SRT is performed on the Novalis, a dedicated linear accelerator. In the first years of the SRT program the main focus of the team was treatment of tumors in the brain. The purpose was to apply optimal techniques with the best achievable accuracy.

In 2004 a specialized SRT team was formed in the department consisting of medical physicists, a medical physics engineer, radiation therapists (RTT's), radiation oncologists and the staff member research and development. In weekly meetings all issues were discussed concerning SRT, including the problems that were encountered in clinical practice and ideas concerning research and development. A database was built to be able to evaluate the treatment results. In this database demographic and treatment related data of all treated patients were recorded. In weekly multidisciplinary tumor boards we discussed the treatment options of patients with primary and secondary brain tumors diagnosed in the Medical Centre Haaglanden in the Hague. Moreover, weekly meetings with diagnostic radiologists were started to discus the target volumes of the neuro-oncology patients for whom stereotactic or conventional radiotherapy was indicated.

Our intention to improve treatment techniques generated several practical questions, such as the question what would be the optimal SRT technique for patients with brain tumors and the question if improvement of patient fixation would be possible. Patients were followed after SRT as long as possible if it was considered in their interest. The results of this follow-up were interesting itself, but again raised questions we wanted to answer. Our first results in patients with brain metastases raised questions about the optimal SRT dose and about lesion growth on post-SRT MRI scans.
This thesis describes the technical and clinical studies we did looking for optimal treatment techniques and looking for improved understanding of the clinical effects in SRT of tumors in the brain.

In **chapter 2a** a planning study is described comparing Intensity Modulated Radiotherapy (IMRT) and Dynamic Conformal Arc (DCA). These two advanced techniques were available for SRT of tumors in the brain when we started the SRT program. However, we were unable to determine which of the two would be preferable in brain tumors with their diverse shapes and sizes. Therefore, we did a comparative planning study in 25 patients with a meningioma or glioma who already had received SRT on the Novalis. The purpose of this planning study was to compare the merits of both techniques. The results would potentially enable us to choose the optimal SRT technique for treating future patients with these brain tumors.

Chapter 2b describes a study aiming to find the optimal fixation method for cranial SRT patients. These patients were initially immobilized with the Brainlab mask system, which included the use of the Upper Jaw Support (UJS). Based on measurements with the Exactrac system we concluded that there was room for improvement. In our department an adaptor to the mask system was developed that included a Vacuum Mouth Piece (VMP). In this study the additional value of the VMP for patient immobilization is determined.

Chapter 3a reports about a clinical study performed in our department looking at the efficacy of SRT of brain metastases. Here we looked at the influence of a number of patient, tumor and treatment related factors on survival and local control probability. The most important question was whether the used treatment protocol resulted in adequate local control rates. However, the relatively low local control rates in the subgroup of patients with large volume

metastases made us decide to initiate another study trying to achieve better results in future patients. This study consisted of a literature review and the evaluation of hypofractionated SRT in patients with large brain metastases.

Chapter 3b describes a literature review that was done to summarize the evidence with respect to the relation of SRT dose and local control probability. A literature search was done over a 20-year period. Although 260 papers were detected that dealt with SRT of brain metastases, only 11 papers could be used to address our research question. Based on this review a dose recommendation could be formulated.

Chapter 3c is the report of a second clinical study performed in our department, assessing the value of hypofractionated SRT of large brain metastases. While performing the analysis interesting additional questions were raised. We noticed more than before that pseudo-progression after SRT was a complicated phenomenon that was not completely described and understood. Therefore, we found it difficult to make clinical decisions in patients with lesion growth after SRT of brain metastases.

The uncertain nature of this pseudo-progression led us to initiate the study described in **chapter 4a**. We used series of co-registered consecutive follow-up MRI scans of patients with pseudo-progression and combined these scans into cine-loops. In this study we used these cine-loops for describing the consecutive events in this radiation induced lesion growth.

Chapter 4b is a study describing the clinical follow-up of 65 patients with progression or pseudo-progression after SRT of brain metastases. The purpose of this study was to assess the clinical course of brain metastasis patients with lesion growth after SRT.

In **chapter 5** the main findings of this thesis are summarized and discussed. Moreover, future perspectives and recommendations concerning treatment delivery and efficacy of stereotactic radiotherapy of intracranial tumors are given.

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CHAPTER 2

Optimizing Treatment

2a: STEREOTACTIC RADIOTHERAPYOF INTRACRANIALTUMORS: ACOMPARISON OF INTENSITY-MODULATED RADIOTHERAPY AND DYNAMIC CONFORMAL ARC

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ABSTRACT

Purpose: Intensity-modulated radiotherapy (IMRT) and dynamic conformal arc (DCA) are two state-of-the-art techniques for linac-based stereotactic radiotherapy (SRT) using the micromultileaf collimator. The purpose of this planning study is to examine the relative merits of these techniques in the treatment of intracranial tumors.

Materials and Methods: SRT treatment plans were made for 25 patients with a glioma or meningioma. For all patients, we made an IMRT and a DCA plan. Plans were evaluated using: target coverage, conformity index (CI), homogeneity index (HI), doses in critical structures, number of monitor units needed, and equivalent uniform dose (EUD) in planning target volume (PTV) and critical structures.

Results: In the overall comparison of both techniques, we found adequate target coverage in all cases; a better mean CI with IMRT in concave tumors ($p = 0.027$); a better mean HI with DCA in meningiomas, complex tumors, and small (< 92 mL) tumors ($p = 0.000$, $p = 0.005$, and $p = 0.005$, respectively); and a higher EUD in the PTV with DCA in convex tumors (gliomas) and large tumors ($p = 0.000$ and $p = 0.003$, respectively). In all patients, significantly more monitor units were needed with IMRT. The results of the overall comparison did not enable us to pre¬dict the preference for one of the techniques in individual patients. The DCA plan was acceptable in 23 patients and the IMRT plan in 19 patients. DCA was preferred in 18 of 25 patients.

Conclusions: DCA is our preferred SRT technique for most intracranial tumors. Tumor type, size, or shape do not predict a preference for DCA or IMRT.

INTRODUCTION

For more than a decade, stereotactic radiotherapy (SRT) has been standard treatment for several intracranial targets. The very high conformality makes it an attractive treatment option, specifically for solitary metastases, benign tumors, targets close to critical structures, and for reirradiation. Fractionated treatments have become a possibility with the development of linac-based SRT and relocatable head frames. At present, several treatment techniques are available in linacbased SRT, but in an individual case the best choice for one or other of these techniques is not always obvious, in spite of several planning studies that have been published [1–6].

Dynamic conformal arc (DCA) and intensity-modulated radiotherapy (IMRT) techniques have become available in SRT with the introduction of the micromultileaf collimator. Two comparative planning studies conclude that DCA is to be preferred for small lesions up to 2 cm^3 [2, 3]. Few studies, however, have addressed the relative merits of both techniques in the treatment of more complex intracranial tumors. For larger and irregularly shaped lesions, adequate treatment plans can be made using IMRT, but the place of DCA in these situations needs further clarification. Moreover, these techniques differ in required workload for quality assurance and the generation of treatment plans (forward planning for DCA and inverse planning for IMRT).

This planning study compares DCA and IMRT in intracranial targets. The purpose of this study is to determine if one of these techniques qualifies as best choice, given the anatomical characteristics of a tumor.

MATERIALS AND METHODS

PATIENTS AND PRESCRIBED TREATMENT

Twenty-five patients with intracranial tumors were selected for this study. We selected patients with targets with different sites, sizes, and shapes to be able to study the relative merits of IMRT and DCA in these different situations. As we wanted to focus on larger targets, we selected patients with a glioma or meningioma and a planning target volume (PTV) larger than 6 cm^3.

Table 1 shows the characteristics of the patients, the tumors, and the prescribed treatments. To be able to study the effect of the PTV shape on the criteria for plan intercomparison, we classified the target shapes into three categories: convex, concave, and complex. All gliomas had a regular convex shape and all but one convexity meningiomas were concave. The base of skull meningiomas were all irregularly shaped, mostly because of extensions in the cavernous sinus and through foramina. This was also the case for a very complex frontal convexity meningioma that extended into the skull base. The shapes of these targets were classified as complex.

To be able to study the effect of the PTV volume, we also classified the targets into two categories based on size: smaller and larger than the median volume of 92 mL.

TREATMENT PLANNING

Each patient was scanned by computed tomography while fixed in the stereotactic head frame (BrainLAB AG, Feldkirchen, Germany). Scans were made with 2-mm slice thickness. A standard upper jaw support provided by Brainlab was used for patients without dentition and for most dentate patients, and a customized vacuum mouth piece was used for some dentate patients [7]. All patients also had an MRI scan (voxel size 1.1 x 1.1 x 1.3 mm^3; T1-weighted with intravenous gadolinium and T2-weighted) of the brain. Coregistration of computed tomography and MRI was done on i-Plan RT Image version 3.0 (BrainLAB).

All contouring was done on i-Plan RT Image version 3.0. The gross tumor volume (GTV)

and the relevant critical structures were contoured on contrast-enhanced MRI scans (T1-weighted MRI with intravenous gadolinium and T2-weighted MRI). In glioma patients, the clinical target volume (CTV) was formed by expanding the GTV with 15 mm, except in regions where natural boundaries precluded microscopic tumor spread. In meningioma patients, we did not use any GTV to CTV margin, assuming no microscopic spread beyond the visible tumor. The positioning accuracy of the mask system together with the use of the Exactrac system allows the use of a 2-mm margin between CTV and PTV [7]. For patients in whom the CTV was in close contact with critical structures, the CTV-PTV margin was adapted manually to avoid overlapping of the PTV and these critical structures. Additionally, we contoured the total brain minus the PTV.

Patient nr	Gender	Age	Diagnosis	Site	PTV (cc)	Shape of target	Prescribed dose	Prescription isodose	Critical structures
1	M	46	Glioma (recurrence)	Convexity	29	convex	4 x 8Gy	100%	No
2	M	45	Glioma (recurrence)	Convexity	55	convex	30 x 1.8Gy	100%	No
3	M	57	Glioma (recurrence)	Convexity	102	convex	30 x 1.8Gy	100%	No
4	M	52	Glioma	Convexity	121	convex	30 x 2Gy	100%	No
5	M	61	Glioma	Convexity	146	convex	30 x 2Gy	100%	No
6	F	68	Glioma	Convexity	147	convex	30 x 2Gy	100%	No
7	M	67	Glioma	Convexity	148	convex	30 x 2Gy	100%	No
8	F	55	Glioma	Convexity	152	convex	30 x 2Gy	100%	No
9	M	62	Glioma	Convexity	235	convex	30 x 2Gy	100%	No
10	F	37	Glioma	Convexity	276	convex	30 x 1.8Gy	100%	No
11	M	62	Glioma	Convexity	304	convex	30 x 2Gy	100%	No
12	M	41	Glioma	Brainstem	85	convex	28 x 2Gy	100%	No
13	F	23	Glioma	Brainstem	97	convex	30 x 2Gy	100%	No
14	F	40	Glioma	Brainstem	146	convex	30 x 1.8Gy	100%	No
15	F	60	Meningioma	Skull base	6	complex	28 x 1.8Gy	80%	Optic nerve, Chiasm
16	M	76	Meningioma	Skull base	8	complex	5 x 5Gy	80%	Optic nerve, Chiasm
17	F	42	Meningioma	Skull base	15	complex	28 x 1.8Gy	80%	Optic nerve, Chiasm Brainstem
18	F	72	Meningioma	Skull base	15	complex	28 x 1.8Gy	80%	Optic nerve Chiasm
19	F	57	Meningioma	Skull base	21	complex	28 x 1.8Gy	80%	Optic nerve, Chiasm
20	F	38	Meningioma	Convexity	48	concave	28 x 1.8Gy	80%	No
21	F	36	Meningioma (atypical)	Convexity	66	concave	30 x 1.8Gy	80%	No
22	M	74	Meningioma (atypical)	Convexity	81	concave	30 x 1.8Gy	80%	No
23	F	68	Meningioma	Skull base	87	complex	28 x 1.8Gy	80%	Optic nerve, Chiasm
24	F	62	Meningioma (atypical)	Convexity	92	complex	30 x 1.8Gy	80%	Optic nerve, Chiasm
25	F	37	Meningioma	Skull base	142	complex	28 x 1.8Gy	80%	Optic nerve, Chiasm Brainstem

Table 1. Characteristics of the patients, the tumours and the prescribed treatments.

All treatment plans were made on Brainscan 5.31 (BrainLAB). For every patient, two plans were made for comparison: an inversely planned IMRT plan and a forwardly planned DCA

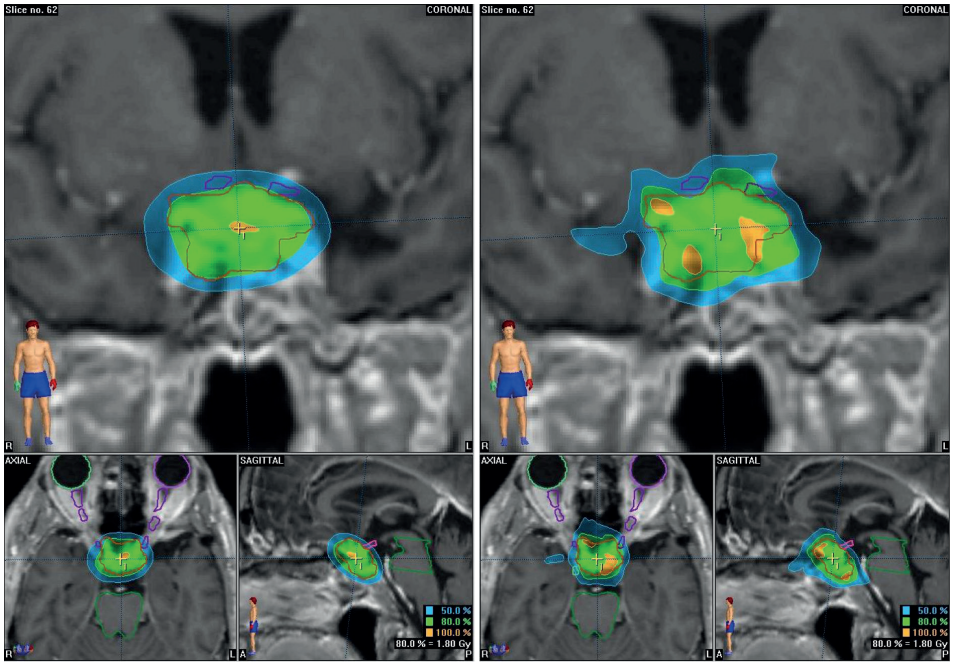

Figure 1. Example of the dose distribution of a patient with a small skull base tumor (Patient 15) with dynamic conformalarc (left) and intensity-modulated radiotherapy (right).

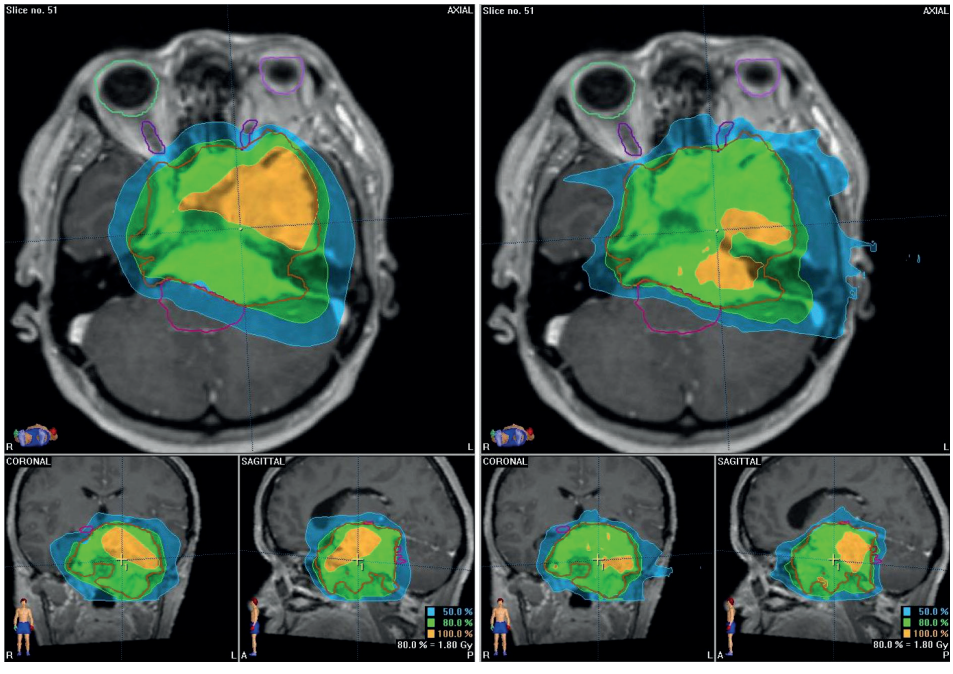

Figure 2. Example of the dose distribution of a patient with a large skull base tumor (Patient 25) with dynamic conformalarc (left) and intensity-modulated radiotherapy (right).

plan (Fig. 1, 2). Calculations of dose–volume histograms were done with a grid size of 2 mm. For small objects, an adaptive grid size was used.
In DCA planning, the critical organs were avoided as much as possible by selecting the optimal table positions, arc angles, and leave positions using the beam's-eye view. In IMRT planning, we did not use a standard set of dose–volume constraints for every patient. In our experience, adaptation of the dose–volume constraints on an individual basis enabled better avoidance of critical organs. Moreover, Brainscan always produces four differentIMRT plans, each with a different balance between the importance given to PTVcoverage and organ-atrisk sparing. For IMRT, manually optimized beam directions were used. The optimal number and orientation of the beams were determined by comparing IMRT plans with varying beam configurations. In all patients, four to six noncoplanar beams yielded a result that was optimal, combined with a realistic treatment time.
Some of the patients were treated with DCA when IMRT was not yet used in clinical practice. For them, IMRT plans were made for this study after they had been treated. For most patients, both DCA and IMRT were available and they were treated according to the plan that was considered preferable.

PLAN COMPARISON

Criteria. Treatment plan intercomparisons were performed using the following criteria: target coverage, conformity index, homogeneity index, and dose in critical organs. To gain more insight into the effect of inhomogeneous dose distributions, the equivalent uniform dose (EUD) in the PTV and critical organs were derived from the dose–volume histogram [8]. Furthermore, the number of monitor units necessary for each plan was recorded.

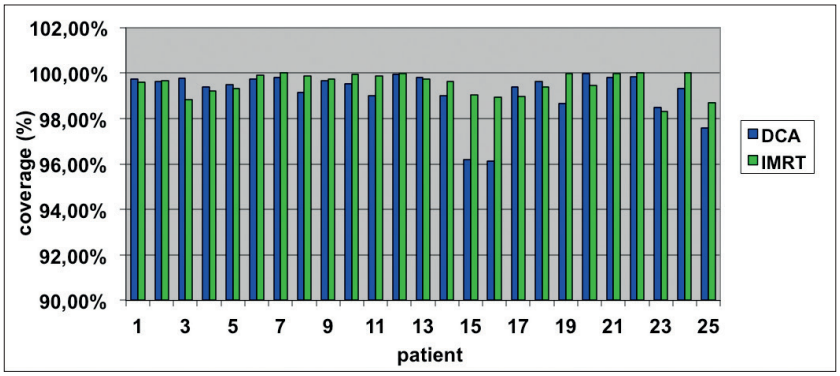

Figure 3. The target coverage of both the dynamic conformal arc and the intensity-modulated radiotherapy plans.

In all plans, 100% of the dose was in the isocenter. Target coverage was defined as the percentage of the PTV covered by the 80% isodose in meningiomas and the 95% isodose in gliomas. The planning goal always was 100% target coverage; a coverage of less than 95% was not accepted.
The conformity index (CI) was defined as in Brainscan as:

$$CI = 1 + V_n/V_t$$

where V_n is the volume of normal tissue receiving the prescribed dose and V_t is the volume of the target receiving the prescribed dose (or 95% of the prescribed dose in gliomas). The ideal CI is 1, a CI higher than 1.5 was considered insufficient, and a CI higher than 2 was

not accepted. As Vn, we used in this formula the volume of total brain minus PTV.
The homogeneity index (HI) was defined for stereotactic radiotherapy as:

$$HI = D_{max}/D_{prescribed}$$

where D_{max} and $D_{prescribed}$ are the maximum and the prescribed dose, respectively. The ideal HI depends on the prescription isodose. When the dose is prescribed to the 80% isodose, the ideal HI is 1.25. Following the principles of stereotactic radiotherapy, the HI should preferably be below 2; between 2 and 2.5 would be acceptable [9].
Analogous with this, for the glioma plans that are prescribed to 100% and for which the 95% isodose should encompass the PTV, we define the HI as:

$$HI = D_{max}/D_{95\%}$$

Dose prescription in gliomas was done using the International Commission on Radiation Units and Measurements (ICRU) criteria, because the CTV usually contains normal brain tissue where hotspots should be avoided. However, we accepted small hotspots (within 7% of the PTV) between 107% and 110%, with a corresponding HI value up to 1.16 [10].
Only patients with meningiomas (who had the dose specified to the 80% isodose) had critical structures close to the target. Only the optic nerve closest to the PTV was considered. The other optic nerve either received a lower dose, or was not classified as a critical structure (in one patient who almost lost the vision of the left eye because of tumor encasement of the left optic nerve).
As clinical dose constraints, we defined
• for the brainstem: 60 Gy maximum point dose and 56 Gy in not more than 2% of the volume.
• for the optic nerves and the optic chiasm: 56 Gy maximum point dose and 50 Gy in not more than 2% of the volume (or 25 Gy maximum point dose in the patient who received 5 x 5 Gy).

However, the planning goal was always the lowest achievable dose in the critical organs.
The EUD was calculated using the equation:

$$EUD = (1/N \sum_i D_i^a)^{1/a}$$

where N is the number of voxels in the anatomic structure of interest, D_i is the ith voxel, and a is the tumor or normal tissue-specific parameter describing the dose–volume effect [11].
We used in the equation as parameter a: –8 for PTV, 4.6 for brainstem, and 7.4 for optic nerve and chiasm [8].
The EUD in the PTV and organs at risk were calculated. In a comparison of different plans, the preferable plan is the one with the highest EUD for the PTV or the lowest EUD for normal tissue and critical structures.

OVERALL COMPARISON OF THE TECHNIQUES

The merits of both techniques were compared for the entire patient cohort. For this comparison, all mentioned criteria were used. The dose in the critical organs was only considered if it was unacceptably high. Furthermore, we compared the techniques according to the diagnosis (glioma or meningioma) and the size and shape of the target.

INDIVIDUAL COMPARISON OF THE TECHNIQUES

We also compared DCA with IMRT for each patient and classified the plans as acceptable or unacceptable, based on the previously mentioned criteria. All plans had been visually inspected and were judged as optimal for the applied technique. If both plans were acceptable, one

of the techniques could be preferable in case of a clear difference with respect to one or more of the criteria. Our preference for one of the two plans was mostly based on the assessment of the CI, HI, and dose in the critical structures. A difference of the CI or the HI of more than 5% (of the mean value for DCA and IMRT) resulted in a preference for the technique with the best index, unless there was a difference in the dose in the critical structures that was considered clinically relevant. Our preference was based much less on visual inspection, which we did not find very useful for comparison of optimal plans, or target coverage. In cases without a clear difference between the plans, we preferred DCA.

STATISTICS

For the statistical analysis we used SPSS, version 16 (SPSS Inc., Chicago, IL). To analyze the differences between the DCA and IMRT plans for each of the previously described criteria, a paired samples t test was used. The same method was applied to various groups of patients classified according to diagnosis, size, or shape of the PTV. The level of statistical significance was considered $p < 0.05$ for all calculations; therefore, a 95% confidence interval was applied.

RESULTS

OVERALL COMPARISON OF THE TECHNIQUES

Target coverage. Figure 3 shows the target coverage of both the DCA and the IMRT plans of all patients. With both techniques, acceptable target coverage was possible in all patients. It was higher than 99% in every plan of the 14 glioma patients and higher than 96% in every plan of the 11 meningioma patients. The mean coverage with the DCA and IMRT plans was 99.1% and 99.5%, respectively. This difference was statistically significant ($p = 0.048$).

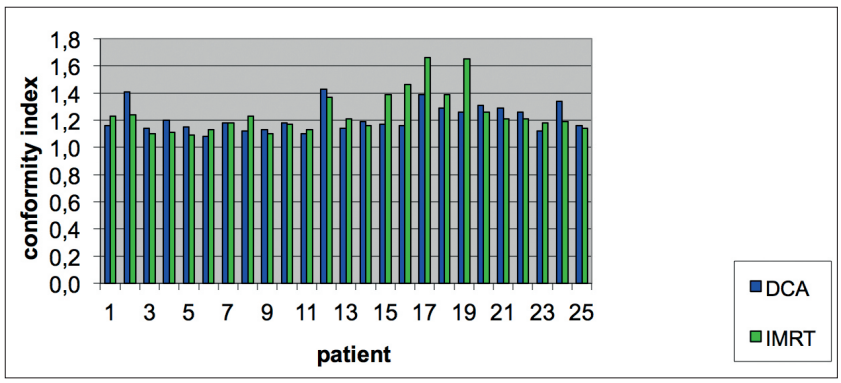

Figure 4. The conformity indices of both the dynamic conformal arc and the intensity-modulated radiotherapy plans.

Conformity. Figure 4 shows the conformity index for total brain minus PTV of all patients using both treatment techniques. The CI of all patients was well below the value two with both techniques. Table 2 shows the relation of the CI to tumor type, shape, and size. For the entire patient group, there was no statistically significant difference between both techniques with respect to mean CI ($p = 0.241$). The mean CI in concave tumors was significantly better with IMRT ($p = 0.027$). However, only 3 patients had concave tumors; therefore, statistics should be interpreted with caution.

Homogeneity. Figure 5 shows all homogeneity indices and Table 2 shows the relation of the HI to tumor type, shape, and size. There was no statistically significant difference between the mean homogeneity indices of DCA and IMRT for all patients ($p = 0.234$). In meningiomas

and complex-shaped tumors, the mean HI was significantly lower with DCA (p = 0.000 and p = 0.005, respectively). In smaller tumors, DCA plans had a lower mean HI than IMRT, but in larger tumors there was no significant difference.

EUD. Figure 6 shows the EUDs of the PTV and total brain minus PTV for all patients. Table 2 shows the relation of the EUD in the PTV to tumor type, shape, and size. For the entire patient group, no significant difference existed between the mean EUDs in the PTV of DCA and IMRT (p = 0.112). Convex tumors (the same cohort as the gliomas) and large tumors had a higher mean EUD with DCA than with IMRT (p = 0.000, and p = 0.003, respectively). These were the categories without significant differences with respect to HI and CI.

	Homogeneity index			Conformity index			Extrapolated uniform dose (Gy)		
	DCA mean (SD)	IMRT mean (SD)	p	DCA mean (SD)	IMRT mean (SD)	p	DCA mean (SD)	IMRT mean (SD)	p
Entire patient group (n=25)	1.221 (0.083)	1.237 (0.126)	0.234	1.214 (0.100)	1.248 (0.157)	0.241	57.7 (9.5)	56.8 (9.7)	0.112
Gliomas (n=14)	1.154 (0.036)	1.130 (0.020)	0.095	1.186 (0.105)	1.175 (0.077)	0.573	57.7 (7.7)	56.0 (7.45)	**0.000**
Meningiomas (n=11)	1.306 (0.023)	1.374 (0.030)	**0.000**	1.250 (0.086)	1.340 (0.186)	0.127	57.7 (11.9)	57.8 (12.3)	0.958
Convex tumours (n=14)	1.154 (0.036)	1.130 (0.020)	0.095	1.186 (0.105)	1.175 (0.077)	0.573	57.7 (7.7)	56.0 (7.5)	**0.000**
Complex shaped tumours (n=8)	1.304 (0.026)	1.364 (0.024)	**0.005**	1.236 (0.098)	1.383 (0.204)	0.056	55.3 (13.3)	54.9 (13.3)	0.782
Concave tumours (n=3)	1.313 (0.015)	1.400 (0.035)	0.093	1.287 (0.025)	1.227 (0.029)	**0.027**	64.0 (2.2)	65.5 (3.5)	0.412
Small tumours (<92cc) (n=12)	1.263 (0.073)	1.318 (0.113)	**0.005**	1.271 (0.104)	1.354 (0.166)	0.130	54.7 (13.1)	54.4 (13.4)	0.797
Large tumours (92cc or more) (n=13)	1.183 (0.074)	1.163 (0.086)	0.215	1.162 (0.064)	1.149 (0.045)	0.504	60.4 (2.8)	58.9 (3.5)	**0.003**
Optic nerve (n=8)							28.8 (12.0)	29.5 (10.8)	0.785
Chiasm (n=8)							30.9 (11.3)	29.4 (15.3)	0.561

Table 2. Overall comparison of the techniques.
Homogeneity index, conformity index and EUD in the PTV with both techniques in relation to tumour type, shape and size. EUD in the critical structures with both techniques. Values that are statistically signifcant are in bold.

ORGANS AT RISK

Table 3 shows the D_{max} (maximum point dose), the D_2, D_{30}, D_{80} (dose exceeded in 2%, 30%, and 80% of the volume), and the EUD of the critical structures. In 3 patients [15, 18, and 25) neither technique completely matched the constraints. The mean EUD in the critical structures did not differ significantly between both techniques (Table 2).

Figure 7 shows the mean dose–volume histogram of brain minus PTV in both the DCA and the IMRT plans. There was no statistically significant difference between both techniques with respect to the dose in brain minus PTV (p = 0.611).

MONITOR UNITS

For comparison of the plans, the IMRT/DCA ratio of the number of monitor units needed was recorded for each patient. The mean IMRT/DCA ratio of the number of monitor units was 2.2 (SD 0.4). In all patients, significantly more monitor units were needed for IMRT plans than for DCA plans.

INDIVIDUAL COMPARISON OF THE TECHNIQUES

Table 4 shows the comparison of the plans of all individual patients with both techniques. Based on this comparison, DCA was preferred in 18 patients and IMRT in 7 patients.
We found that the preference for one of the techniques in the individual patients could not be predicted from the overall comparison based on diagnosis, shape, or size of the tumors.

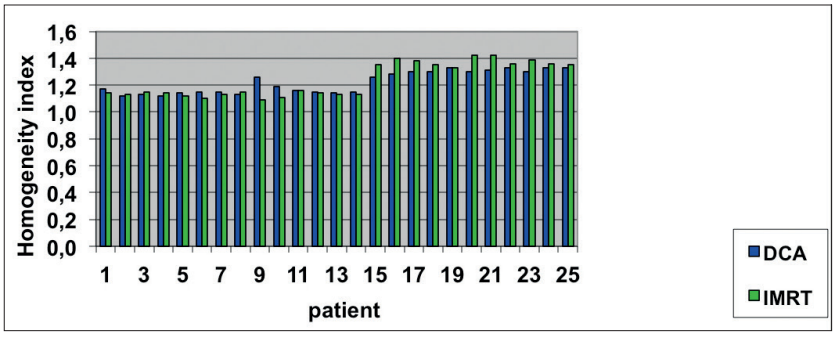

Figure 5. The homogeneity indices of both the dynamic conformal arc and the intensity-modulated radiotherapy plans.

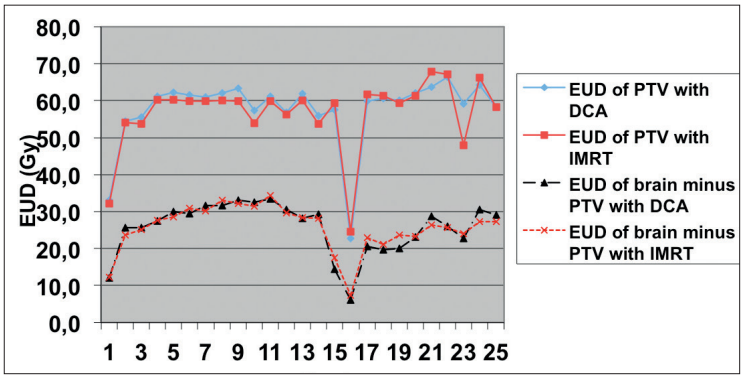

Figure 6. Equivalent uniform dose of the planning target volume (PTV) and total brain minus PTV with both the dynamic conformal arc and the intensity-modulated radiotherapy plans.

DISCUSSION

This study compared IMRT and DCA in intracranial tumors of various sites, sizes, and shapes. In the overall comparison of both techniques, we found adequate target coverage in all cases and differences in mean CI, HI, and EUD in subgroups. In all patients, significantly more monitor units were needed for IMRT plans than for DCA plans. The DCA plan was acceptable in 23 patients and the IMRT plan in 19 patients. DCA was preferred in 18 of the 25 patients.
Only a few studies comparing DCA and IMRT for brain tumors have been published. Ding *et al.* performed a planning study in 15 patients comparing three-dimensional conformal radiotherapy, DCA, and IMRT for stereotactic brain tumor treatment [3]. The authors' conclusion is similar to ours, namely that DCA is suitable for most cases in stereotactic brain tumor treatment. However, we do not agree with their conclusion that IMRT plans are the best in larger tumors. Their results in tumors larger than 100 mL are based on only 2 patients,

whereas we studied 11 patients with tumors larger than 100 mL.
The group of the University of Erlangen compared DCA and IMRT in pituitary tumors and small skull base tumors [1, 2]. They concluded that DCA was to be preferred in these small skull base tumors (until 10.4 cm3) [2]. However, for pituitary tumors, IMRT was superior in their hands [1]. The discrepancy between the conclusions in both papers is not fully explained. Because DCA is a forwardly planned technique, the experience of the planner to some extent determines the quality of the plan and thus also influences the result of a comparative planning study.

Case	PTV dose (Gy)	Optic nerve					Chiasm					Brainstem				
		D_{80}	D_{30}	D_2	D_{max}	EUD (Gy)	D_{80}	D_{30}	D_2	D_{max}	EUD (Gy)	80	30	2	D_{max}	EUD (Gy)
15	DCA	3.9	13.4	50.0	**56.1**	34.3	18.6	39.6	51.0	54.2	40.3					
	IMRT	3.2	12.4	**54.8**	**58.6**	38.8	18.3	46.8	55.7	**58.6**	45.4					
16	DCA	0.5	10.8	17.2	20.9	10.1	6.4	9.8	15.9	18.1	9.3					
	IMRT	0.9	10.3	16.6	20.3	9.7	4.0	8.8	15.2	17.8	8.8					
17	DCA	1.3	4.2	16.4	25.8	12.3	12.9	31.2	41.7	45.4	32.0	17.2	31.1	47.0	52.9	32.0
	IMRT	3.2	10.7	32.4	38.4	23.0	10.0	29.1	48.4	52.9	35.5	5.2	12.9	40.3	50.4	23.0
18	DCA	4.5	37.2	**52.0**	**56.7**	39.3	25.8	35.5	45.6	50.4	36.1					
	IMRT	8.4	39.7	**54.3**	**58.0**	42.1	14.7	28.9	47.3	52.9	34.3					
19	DCA	2.6	5.9	41.0	46.0	27.9	17.6	28.9	42.2	47.3	31.7					
	IMRT	10.4	17.0	**50.8**	54.8	34.4	10.1	26.9	43.7	48.5	32.5					
23	DCA	38.4	44.0	47.7	49.8	43.0	20.3	24.9	31.7	34.0	25.4					
	IMRT	9.5	29.6	42.6	47.3	32.0	5.0	6.8	10.7	14.5	8.2					
24	DCA	18.9	32.0	47.3	51.3	35.2	22.1	25.7	31.1	33.1	25.8					
	IMRT	19.9	30.2	47.9	**57.4**	35.1	16.3	19.9	28.3	31.7	21.5					
25	DCA	15.3	25.5	38.9	44.7	28.5	43.1	47.3	51.7	54.2	46.7	26.6	41.2	51.7	**60.5**	39.3
	IMRT	8.9	12.4	29.3	40.3	21.2	44.1	50.0	55.1	57.3	49.0	20.2	41.7	55.9	**61.1**	40.6

Table 3. Doses in the critical structures
Abbreviations: DCA = dynamic conformal arc; IMRT = intensity-modulated radiotherapy; PTV = planning target volume; D_{max} = maximum point dose ; D_2 = dose exceeded in 2% of the volume of the structure; D_{30} = dose exceeded in 30% of the volume of the structure; D_{80} = dose exceeded in 80% of the volume of the structure. Values that do not match the constraints are in bold.

IMRT and DCA have both been compared with other stereotactic techniques in brain tumors. Perks *et al.* compared DCA with gamma knife radiosurgery in acoustic neuromas [12]. They found a slightly better conformity index for gamma knife, but a more homogeneous dose distribution for DCA. They concluded that both techniques had advantages and disadvantages. Nakamura *et al.* compared gamma knife radiosurgery with IMRT in small and medium sized skull base tumors [13]. They found that IMRT was better in almost all aspects. Baumert *et al.* compared IMRT with conformal beam in skull base meningiomas [6]. IMRT was superior in almost all aspects, especially in large and irregular targets. IMRT was also compared with tomotherapy; neither technique seemed clearly superior to the other [4, 14].
In our opinion, dose homogeneity is an important aspect of plan quality, although it does not always receive attention in planning studies [4, 6]. In our patients with tumors smaller than 92 mL, the mean HI was better with DCA than IMRT. In a study comparing DCA and IMRT in very small skull base tumors, Ernst-Stecken *et al.* also report lower HI with DCA compared with IMRT [2]. Dose gradients can be important when normal structures such as cranial nerves or the carotid artery are in the PTV. For this reason, we consider the lower mean HI in meningiomas/complex tumors with DCA to be an advantage. In some individual patients, a high HI even caused the rejection of a plan as unacceptable. The char-

acterization of dose homogeneity is not complete with HI only. We found that some patient categories without any difference in mean HI and CI (gliomas/convex tumors/ larger tumors) had a significantly higher mean EUD with DCA. The type of dose distribution between the maximum dose and the prescription dose may explain this higher EUD with DCA. However, we did not base any clinical decision on the EUD values, because the EUD concept has not gained general acceptance and because of the uncertainty of the values of the parameter for the different organs.

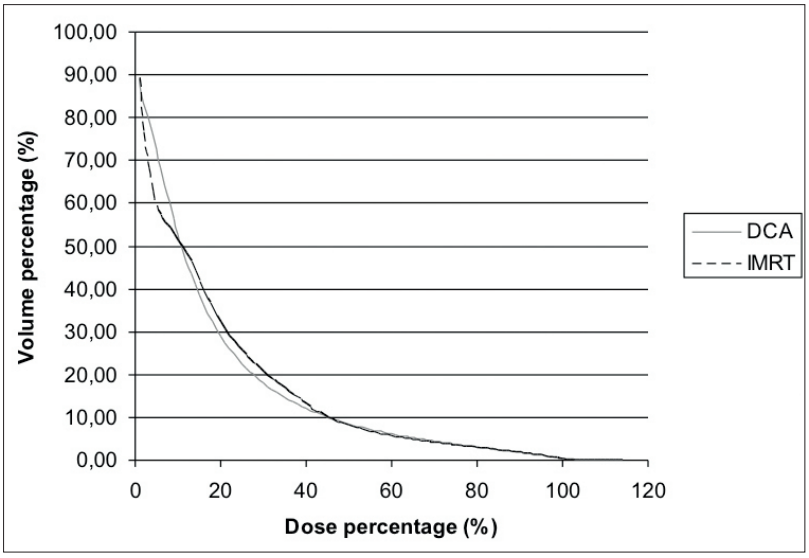

Figure 7. Mean dose–volume histogram of brain minus planning target volume in both the dynamic conformal arc and the intensity-modulated radiotherapy plans.

Gliomas have been treated following the ICRU guidelines to avoid large inhomogeneities, because the target not only contains tumor, but also normal brain with microscopic tumor extensions [15]. Still, the criteria for dose homogeneity of the ICRU were not met in the glioma patients, for whom we had to accept small hotspots up to 110%. In this study, the HI definition, originally devised for radiosurgery, had to be adopted for this patient group by taking the 95% isodose in the formula for the prescribed dose [9]. In doing so, the HI would be acceptable up to 1.16. The question can be asked if the ICRU guidelines are appropriate for techniques such as IMRT and DCA. Das *et al.* report a retrospective analysis of 803 patients with tumors in brain, head and neck, or prostate treated with IMRT [10]. The maximum dose was more than 10% higher than the prescribed dose in 46% of these patients. They also report substantial variation in prescribed and administered dose among institutions.

Several different conformity indices are proposed in the literature [16]. We decided to use the definition from Brainscan, because it gives information about the volume of healthy tissue receiving the prescribed dose. This CI is only informative if the target coverage is adequate, which was the case in all patients with both techniques. The mean CI was only different in concave tumors, where IMRT was better. However, this difference was considered clinically relevant in only 1 patient. In most cases, CI was adequate for both techniques and in only 2 patients, with small complex tumors, CI was unacceptable with IMRT.

Sparing the optic system is a challenge when the tumor is in close contact with it, as was the case in eight of the patients. It is uncertain what dose can be accepted as safe for the optic nerves or chiasm. Most information comes from series with homogeneous dose distributions in the optic system [17, 18]. A dose below 56 Gy in 2-Gy fractions seems safe. However, in

stereotactic radiotherapy, very sharp dose gradients exist in or close to the optic system. In these situations, the question arises if a higher point dose or a higher dose in part of the organ at risk may be accepted. But one could also argue that the radiation tolerance of an optic nerve compressed by a tumor for longer periods may be less than that of an uncompressed nerve. Therefore it is our opinion that it is safest to keep the dose in the optic nerve or chiasm below 50 Gy and to accept 56 Gy in not more than 2% of its volume. When the tumor is in contact with the optic system, the choice between optimal target coverage and higher dose in the optic system may have to be taken.

Patient	Coverage DCA	Coverage IMRT	CI DCA	CI IMRT	HI DCA	HI IMRT	Critical Structures DCA	Critical Structures IMRT	Acceptable plan	Preferred plan
1	+	+	+	+	+	+	+	+	Both	DCA
2	+	+	+	+	+	+	+	+	Both	IMRT
3	+	+	+	+	+	+	+	+	Both	DCA
4	+	+	+	+	+	+	+	+	Both	IMRT
5	+	+	+	+	+	+	+	+	Both	IMRT
6	+	+	+	+	+	+	+	+	Both	DCA
7	+	+	+	+	+	+	+	+	Both	DCA
8	+	+	+	+	+	+	+	+	Both	DCA
9	+	+	+	+	-	+	+	+	IMRT	IMRT
10	+	+	+	+	-	+	+	+	IMRT	IMRT
11	+	+	+	+	+	+	+	+	Both	DCA
12	+	+	+	+	+	+	+	+	Both	DCA
13	+	+	+	+	+	+	+	+	Both	DCA
14	+	+	+	+	+	+	+	+	Both	DCA
15	+	+	+	+	+	+	-	-	None	DCA
16	+	+	+	+	+	+	+	+	Both	DCA
17	+	+	+	-	+	+	+	+	DCA	DCA
18	+	+	+	+	+	+	-	-	None	DCA
19	+	+	+	-	+	+	+	-	DCA	DCA
20	+	+	+	+	+	+	+	+	Both	DCA
21	+	+	+	+	+	+	+	+	Both	IMRT
22	+	+	+	+	+	+	+	+	Both	DCA
23	+	+	+	+	+	+	+	+	Both	IMRT
24	+	+	+	+	+	+	+	-	DCA	DCA
25	+	+	+	+	+	+	-	-	None	DCA

Table 4. Plan comparison for all individual patients.
Abbreviations: DCA = dynamic conformal arc; IMRT = intensity-modulated radiotherapy; CI = conformity index. + Defined criteria or constraints are met. – Defined criteria or constraints are not met. * In Patients 15, 18, and 25, none of the techniques fully matched the dose constraints in the critical organs, but in all 3 patients DCA plan was accepted in clinical practice, because the doses in the critical organs were close to the maximum allowed doses.

In all patients, more monitor units were needed for the IMRT plans than for the DCA plans. IMRT is expected to cause more secondary malignancies compared with three-dimensional conformal radiotherapy through two mechanisms: the first is more monitor units with IMRT and the second is the exposure of a larger volume of normal tissue to low radiation doses in IMRT [19]. In this comparison of IMRT with DCA, we did find that more monitor units were needed with IMRT, but we did not find a statistically significant difference between both techniques with respect to the volume of irradiated brain tissue (Fig. 7). Although there is no proof of the relation between the number of monitor units and the risk of radiation-

induced malignancies, in our opinion the difference in monitor units needed is an important argument in favor of DCA, when plans are comparable in other aspects.
In conclusion, we prefer DCA as SRT technique for most intracranial tumors. Tumor type, size, or shape does not predict a preference for a DCA or IMRT plan. If the patient's IMRT and DCA plans are comparable, we prefer DCA, because less time-consuming quality assurance is needed and fewer monitor units are used with DCA than with IMRT. Our policy is to start making a DCA plan for all patients with intracranial tumors, only proceeding to an IMRT plan if the DCA plan is unacceptable or if we expect a significant improvement.

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2b: POSITIONING ACCURACY IN STEREOTACTIC RADIOTHERAPY USING A MASK SYSTEM WITH ADDED VACUUM MOUTH PIECE AND STEREOSCOPIC X-RAY POSITIONING

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ABSTRACT

Purpose: For cranial patients receiving stereotactic radiotherapy, we use the Exactrac stereoscopic X-ray system to optimize patient positioning. Patients are immobilized with the BrainLAB Mask System (BrainLAB, Feldkirchen, Germany).We have developed an adapter to this system that accommodates a vacuum mouth piece (VMP). Measurements with the Exactrac system have been performed to study the positioning accuracy after corrections with this system and to evaluate the accuracy of the VMP vs. the standard available upper jaw support (UJS).

Methods and Materials: Positioning results were collected for 20 patients with the UJS and 20 patients with the VMP, before treatment (1122 fractions) and after treatment (400 fractions). For all 6 degrees of freedom the average, the random error and systematic error were calculated.

Results: The average vector length before and after correction with the Exactrac system was 2.1 ± 1.2mm and 0.7 ± 0.6mm respectively for UJS and 1.7 ± 0.7mm and 0.4 ± 0.4mm for VMP. Interfraction positioning for translations was greatly improved after correction with the Exactrac system ($p < 0.0005$) and is better with VMP than with UJS ($p = 0.005$). Outliers were greatly reduced. Interfraction rotations were significantly smaller for VMP. Intrafraction errors for vertical and longitudinal translations and for rotations were smaller for the VMP.

Conclusions: Positioning correction using the Exactrac X-ray system greatly improves accuracy. Adding the VMP results in even better patient fixation and smaller rotations, making it a useful addition to the Mask System. Combined, this is a convenient and accurate alternative to invasive fixation methods.

INTRODUCTION

Several systems are used clinically to position and immobilize patients for stereotactic treatments, either for single fraction treatments or for fractionated treatments. Originally only invasive frames were used, and only radiosurgery (singlefraction, high-dose treatment) was applied. The accuracy of these invasive systems is considered to be optimal, as the patient cannot move relative to the coordinate system of the frame. It is argued however, that also invasive stereotactic frames have limited accuracy [1, 2].
Later several noninvasive, relocatable stereotactic immobilization systems have been developed [3–5], mainly to make fractionated treatments possible and to improve patient comfort. Cranial patients at our institution who are treated at the Novalis (BrainLAB, Feldkirchen, Germany) are immobilized with the BrainLAB Mask System. Based on measurements using the BrainLAB Exactrac system in 9 patients who received fractionated treatment, we concluded that there was room for improvement: we found deviations of up to 3.0 mm in the longitudinal direction and up to 2.5 mm in the other directions, which we considered to be too great for stereotactic treatment. These findings are in agreement with Alheit *et al.* [3] and Baumert *et al.* [6]. Therefore we developed an adapter to the Mask System that accommodates for a vacuum mouth piece (VMP, part of the Head Fix system from Medical Intelligence, Schwabmünchen, Germany). The VMP is a customized bite block that is individually molded for each patient and fixed to the palate by applying vacuum.
Our Novalis accelerator is equipped with the Exactrac stereoscopic X-ray positioning system. The Exactrac system can be used to measure the accuracy of patient positioning and to correct deviations. Exactrac measurements have been performed with patients immobilizedwith the Mask System with either the Upper Jaw Support (UJS) or the VMP. The UJS is an L-shaped metal strip attached to the frame of the mask system that presses against the upper teeth. The UJS is a standard BrainLAB option for use with the Mask System. In this study the VMP system is described and its accuracy is compared to that of the original UJS system. The results of accuracy measurements with these two systems before and after correction with the Exactrac system are presented here. To assess intrafraction stability, measurements were also performed at the end of treatment.

METHODS AND MATERIALS

At our institution, cranial patients treated at the Novalis have always been immobilized using the BrainLAB Mask System. This system consists of a U-shaped frame to which three layers of thermoplastic material are attached. These layers are moulded into the shape of the patients head. In addition to this, an UJS is used, meant to provide a reproducible touch for the patient's teeth (Fig. 1). This should improve the accuracy of patient positioning, especially in the longitudinal direction [6].

EXACTRAC SYSTEM

To assess the accuracy of the patient positioning using the mask system, we performed measurements using the BrainLAB Exactrac stereoscopic X-ray system [7]. This system uses two fixed X-ray sources and two corresponding image detectors. The images that are taken with this system are registered to digital reconstructed radiographs (DRRs). These DRRs are calculated online (during the registration procedure) from the planning-CT data. Many DRRs are calculated for different small translations in the x, y, and z directions and rotations around the x, y, and z axes. The DRR with the optimal registration result gives the positional deviation for both translations and rotations.
The translational deviation found this way can be corrected by automatic couch movement.
We performed a study, using a human skull phantom with an inserted lead marker, to measure

the accuracy of the Exactrac system for this application. The skull phantom was scanned by computed tomography and a treatment plan was made with the isocenter in the center of the lead marker. This isocenter was transferred to the Exactrac system. The skull phantom was positioned in the isocenter and correct positioning was verified using portal film. Well-known position deviations (both for translations and for rotations) were then set up, and the Exactrac result was compared with the actual deviations. This was repeated for several combinations of different translations and rotations. We used translations of approximately 3, 5, 10, and 20 mm and rotations of approximately 2°, 3°, and 5°. This study was similar to that of Verellen *et al.* [7].

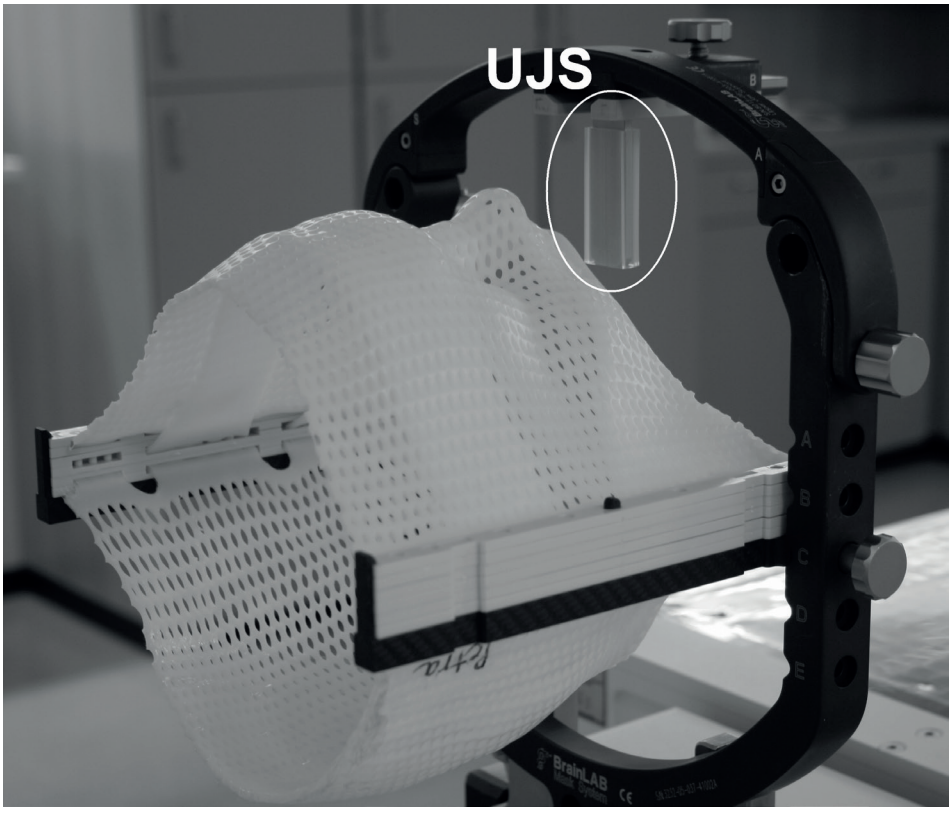

Figure 1. BrainLAB Mask System with Upper Jaw Support.

VACUUM MOUTH PIECE ADAPTER

To improve the positioning, we have developed an adapter to the mask system frame that holds a vacuum mouth piece (VMP). The mouth pieces are obtained from Medical Intelligence. Normally these are used as part of the Headfix system [5].

The adapter was needed because the mouth pieces did not fit directly to the holder for the UJS, which is attached to the U-shaped frame of the Mask System. This gave us the opportunity to incorporate other design goals as follows: a modular design for easy setup; option for rapid assembly; fast release in case of an emergency; incorporation of different degrees of freedom to accommodate for different patient shapes and sizes; and availability of individual, reusable carriages to fix the mouth piece reproducibly in the right position for each patient.

For each patient, an impression of the teeth and the hard palate was made in a dental paste on the mouth piece. Through a small hole, vacuum was applied to the VMP so that it was fixed

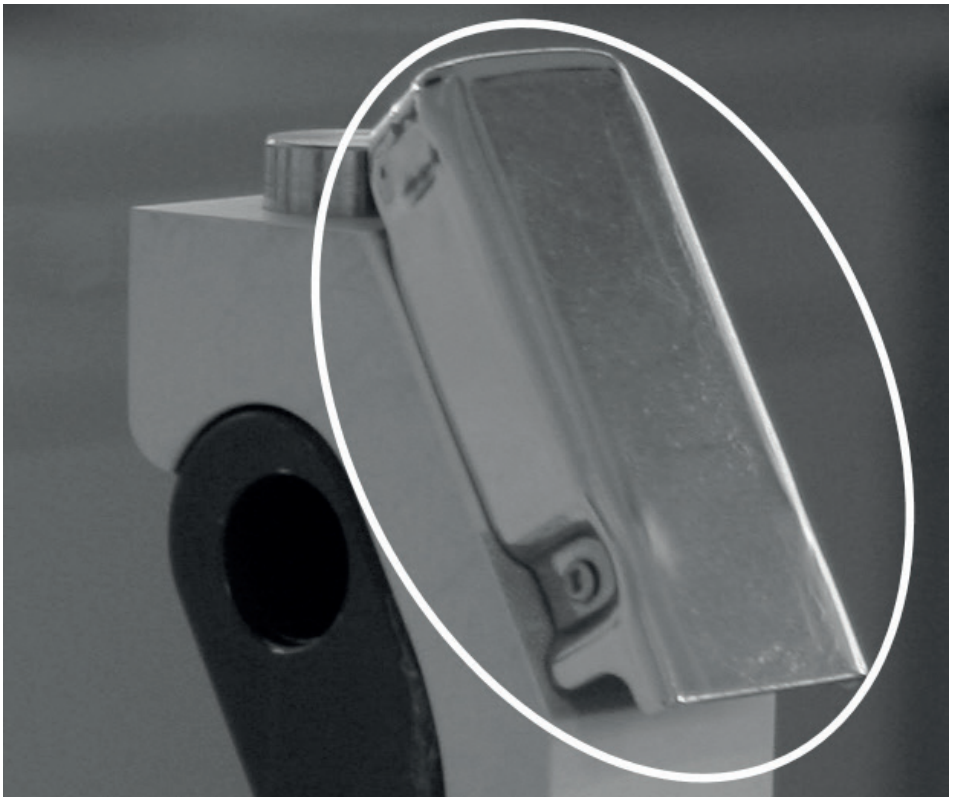

Figure 2. BrainLAB Mask System with VMP. Attachment of adapter to U-shaped frame. The quick release is indicated in the ellipsis.

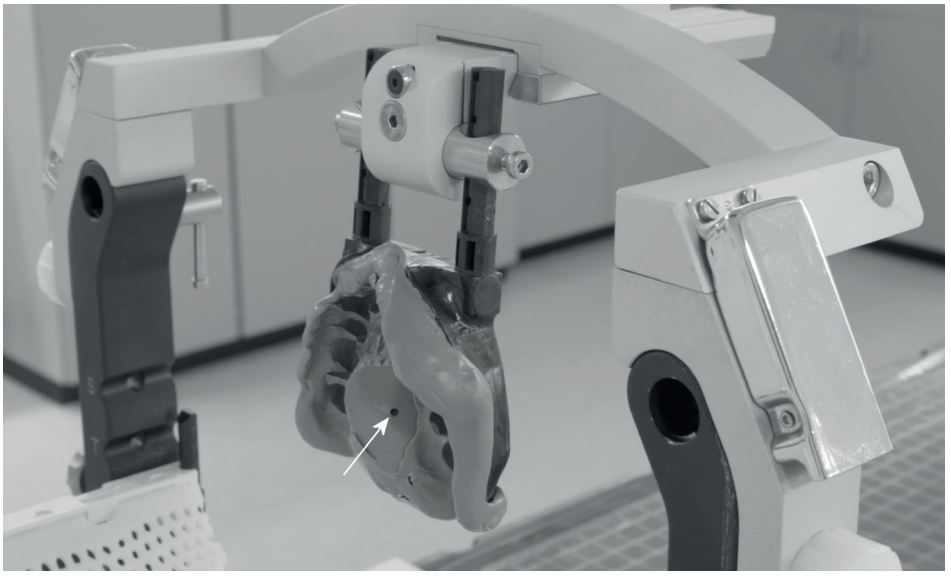

Figure 3. BrainLAB Mask System with VMP. Adapter with carriage attached to the U-shaped frame. The vacuum hole is indicated by the arrow.

without the patient actively having to bite to it. The VMP was fixed to the carriage that can be reproducibly positioned in the adapter using a scale.
The mouth piece adapter consists basically of four parts: two identical posts that can be attached to the U-shaped frame of the Mask System using screws (Fig. 2). The main piece of the adapter can be attached to these posts (Fig. 3). This piece is accurately positioned on the posts using indexing pins. With quick releases the piece is secured to the posts. This assures fast and accurate assembly and disassembly. The shape of the adapter is such that enough space is available for the mouth piece itself.

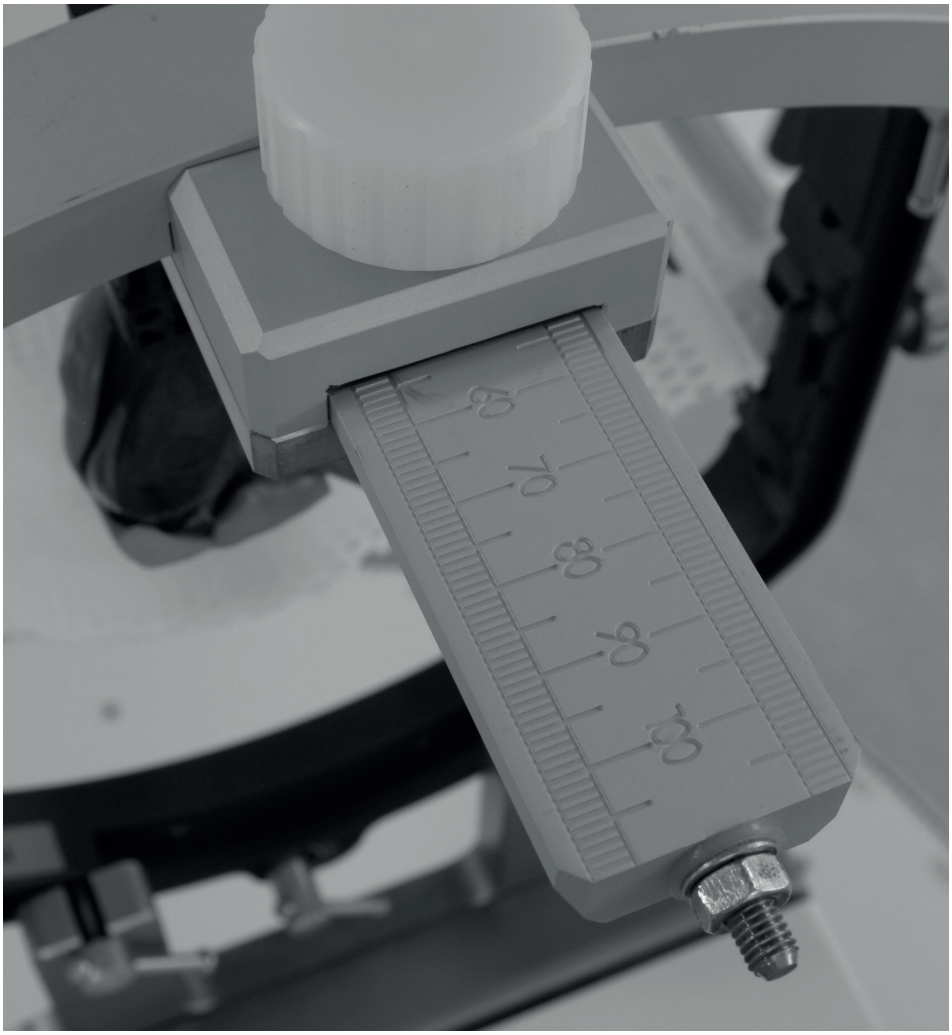

Figure 4. BrainLAB Mask System with VMP. Carriage with scale.

Twelve carriages (in two different sizes) have been manufactured that hold the mouth pieces in such a way that they can be rotated in two different directions and can be moved up and down. When a suitable position is found for a patient, this position can be fixed for the duration of the radiotherapy course. The carriage slides into the adapter and can be moved in the correct position by means of a scale (Fig. 4) and then fixed with a screw.

Vacuum is applied through a thin hose that is attached to the mouth piece at the one end and to a standard suction pump at the other end. A small hole is left in the dental mould to accommodate for the vacuum [5].
When using the VMP, extra attention has to be paid to the fitting of the mask to the upper lip because the VMP uses more space there and the exact position of the head is more critical to make sure that the VMP does not interfere with the target positioner box that is used for initial positioning (see below and Fig. 5).

POSITIONING STUDY

Positioning results have been collected for 20 patients with the UJS and for 20 patients (with teeth) with the VMP. The patient groups contained similar patients regarding age, tumor, and performance status (Table 1).

	Upper jaw support			Vacuum mouth piece		
	Age	**Performance status**	**Diagnosis**	**Age**	**Performance status**	**Diagnosis**
	72	70	Meningioma	38	100	Meningioma
	42	90	Meningioma	46	90	Metastasis
	58	90	Glioma	37	100	Glioma
	45	90	Trigeminus Schwannoma	29	100	Neurocytoma
	53	90	Glioma	36	90	Glioma
	68	80	Glioma	61	100	Glioma
	54	80	Glioma	60	90	Meningioma
	57	90	Meningioma	50	90	Glioma
	43	100	Pituitary adenoma	36	100	Meningioma
	41	70	Glioma	68	90	Meningioma
	42	90	Meningioma	78	100	Acoustic neurinoma
	52	100	Craniopharyngioma	61	90	Meningioma
	61	90	Nasopharynx carcinoma	23	70	Glioma
	62	100	Pituitary adenoma	53	80	Glioma
	62	90	Glioma	41	80	Glioma
	48	90	Acoustic neurinoma	41	80	Glioma
	53	70	Pineoblastoma	52	80	Glioma
	60	90	Glioma	16	100	Pituitary adenoma
	62	80	Meningioma	47	100	Pituitary adenoma
	60	90	Glioma	66	90	Pituitary adenoma
Mean	54.8	87.0		47.0	91.0	
SD	9.0	9.2		15.8	9.1	

Table 1. Patient characteristics in study of BrainLAB system with vacuum mouth piece vs. standard upper jaw support.

Position accuracy was assessed immediately after stereotactic setup, after position correction and immediately after irradiation, to investigate initial positioning accuracy and intrafraction motion. The procedure is as follows. Initially patients are positioned based on the target positioner box, on which the isocenter is indicated using printouts of the treatment planning system. After this, Exactrac images are acquired and the position deviation is determined by the Exactrac computer by registering these images to the planning-CT derived DRRs. This result is defined as the initial position deviation. Then the translational part of the position is corrected,

if necessary, and a verification is performed, again using the Exactrac system. If the deviations are sufficiently small, treatment is started. Once a week Exactrac images are acquired, and the position accuracy is determined after treatment completion to assess intrafraction movement. Intrafraction movement is defined as the difference between the verification position and the post-treatment position.

For the patients with UJS a total of 616 fractions were analyzed for initial positioning deviation, 392 for verification positioning deviation (after correction), and 192 for intrafraction movement. For the patients with VMP a total of 519 fractions were analyzed for initial positioning deviation, 294 for verification positioning deviation, and 203 for intrafraction movement. There were fewer results for the verification positioning than for initial positioning because not always corrections were required. The threshold for correction was a vector length of 1 or 2 mm, depending on the vicinity of critical structures.

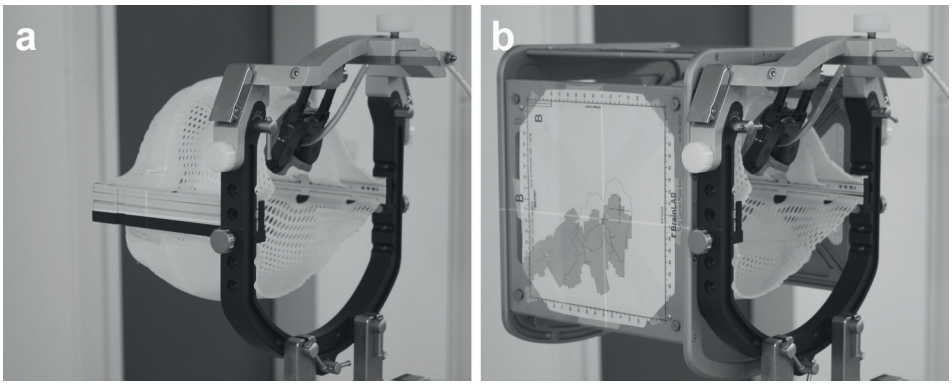

Figure 5. BrainLAB Mask System with VMP. Overview of the complete setup. (a) Without the Target Positioner Box. (b) With the Target Positioner Box.

Several statistical methods have been used in patient positioning studies. In this study we have chosen to analyze the data according to the method of separating inaccuracies in systematic and random errors, according to the method of Bel *et al.* [8], as this method has been shown to give useful results. According to this method, the systematic deviation for a single patient is the mean displacement (relative to the reference position) over all fractions. The random deviation for a single patient is the standard deviation (SD) of the day-to-day variations around this systematic deviation. For a group of patients the systematic error Σ is defined as the standard deviation of the systematic deviations for all patients. The random error σ for a group is defined as the quadratic mean (or root mean square) of the random deviations in the group. A clear description of this method has been published by Stroom and Heijmen [9].

For all 6 degrees of freedom the average over all fractions, the random error and the systematic error were calculated. The results have been analyzed with respect to statistical significance using the *t* test for the averages and for the random errors (σ) and the *F* test for the systematic errors (Σ). The *F* test can be used to test whether the SDs of two distributions are equal.

For the length of the displacement vector also the cumulative distribution is calculated, *i.e.*, the frequency of deviations larger than a specific value (vertically) is plotted against that deviation (horizontally).

RESULTS

EXACTRAC SYSTEM

Based on the phantom study that we have performed, we have concluded that the maximum

deviation of the Exactrac system for cranial applications is 0.7 mm in each direction and 0.5° around each axis. For smaller translations (≤5 mm) and rotations (≤3°) accuracy was even better than 0.3 mm for translations and 0.2° for rotations. Overall the RMS value of the deviations for translations in each direction is 0.4 ± 0.2 mm and for rotations 0.2 ± 0.1°. This is slightly better than reported by Verellen *et al.* [7] and Yan *et al.* [10], possibly because of the good contrast of the skull images and because of the fact that their system at that time only used one image detector, attached to the treatment couch. The couch had to be repositioned in between image captures.

POSITIONING STUDY

The p value for the difference in age between the two patient groups was 0.063 and for the difference in performance status 0.176. Therefore we can conclude that there were no significant differences between the groups in this respect. Differences in positioning results between the two patient groups probably cannot be attributed to differences in patient characteristics. The results of the positioning study are given in Table 2. Differences between the initial positioning accuracy (based on the target positioner box) and on the accuracy of positioning after correction with the Exactrac system were examined. Positioning improvement by use of the Exactrac system was apparent. Systematic and random errors were in the order of 1 mm for the initial translations and of a few tenths of a millimeter after correction, but the values were smaller for the VMP group than for the UJS group. Both for the UJS and for the VMP the differences between initial positioning accuracy and accuracy after position correction were highly significant for almost all translation parameters: only the average values for longitudinal translations were not significantly different. For the average lateral translations with the UJS the p value was 0.003, for all other parameters the p value was ≤0.001. Systematic and random errors for initial rotations and for rotations after correction were approximately 0.4° for the VMP and 0.8° for the UJS. None of the rotational parameters were significantly different between initial positioning accuracy and accuracy after position correction (for all, $p > 0.5$). This makes sense since in this study rotations were not corrected with the Exactrac system. If there were transfer errors between CT, treatment planning and treatment, the average values of translations and rotations would be different from zero. Since these values were all very small, for initial positioning as well as for the corrected positioning and for the UJS as well as for the VMP, we can conclude that there were no systematic transfer errors.

Differences between UJS and VMP concerning inter-fraction positioning accuracy also were evident. For the initial positioning accuracy the differences between the two groups (UJS vs. VMP) were statistically significant for the random errors in vertical and longitudinal translations ($p < 0.001$), the translation vector length ($p = 0.001$) and for rotations around all three axes ($p < 0.002$) and for the systematic errors in lateral translations ($p = 0.025$) and for rotations around the longitudinal and lateral axes ($p = 0.001$). For the positioning after correction the differences were statistically significant for the random errors in longitudinal translations ($p = 0.005$) and for rotations around all three axes ($p = 0.001$ for rotations around the table axis, $p = 0.004$ for rotations around the longitudinal axis and $p < 0.001$ for rotations around the lateral axis) and for the systematic errors in longitudinal translations ($p = 0.012$) and rotations around the longitudinal ($p = 0.005$) and lateral ($p = 0.001$) axes.

In regard to intrafraction motion, systematic and random errors for intrafraction translations were a few tenths of a millimeter but smaller for the VMP than for the UJS. Systematic and random errors for intrafraction rotations were approximately 0.2° for the VMP and 0.5° for the UJS respectively. The differences were statistically significant for the random errors in longitudinal translations ($p = 0.029$) and for rotations around table ($p = 0.013$), longitudinal ($p = 0.010$), and lateral ($p = 0.001$) axes, as well as for the systematic errors in vertical ($p = 0.041$) and longitudinal ($p = 0.002$) translations and rotations around the lateral axis ($p < 0.001$).

		Initial positioning deviation							**Verification images deviation**							**Intra-fraction movement**						
		Translations [mm]				Rotations [°]			Translations [mm]				Rotations [°]			Translations [mm]				Rotations [°]		
		Vertical	**Long**	**Lat**	**Vector**	**Table**	**Long**	**Lat**	**Vertical**	**Long**	**Lat**	**Vector**	**Table**	**Long**	**Lat.**	**Vertical**	**Long**	**Lat**	**Vector**	**Table**	**Long**	**Lat**
Average	VMP	0.40	-0.47	0.58	1.70	0.06	-0.03	-0.42	-0.02	-0.01	0.01	**0.43**	0.02	0.04	-0.39	-0.03	0.13	-0.11	**0.44**	0.06	-0.02	-0.02
	UJS	0.46	-0.01	0.69	2.13	0.18	0.21	-0.41	-0.06	0.08	0.05	**0.66**	0.15	0.22	-0.21	0.01	0.05	-0.11	**0.59**	0.02	0.02	-0.05
Random σ	VMP	**0.48**	**0.95**	0.61	**0.69**	**0.38**	**0.40**	**0.38**	0.29	**0.35**	0.30	0.38	**0.39**	**0.43**	**0.39**	0.21	**0.30**	0.29	0.25	**0.27**	**0.15**	**0.14**
	UJS	**0.78**	**1.47**	0.78	**1.19**	**0.80**	**0.70**	**0.95**	0.41	**0.58**	0.36	0.58	**0.78**	**0.74**	**1.01**	0.26	**0.58**	0.28	0.46	**0.46**	**0.49**	**0.48**
Systematic Σ	VMP	0.45	1.08	**0.50**	0.59	0.49	**0.47**	**0.44**	0.17	**0.25**	0.10	0.20	0.52	**0.47**	**0.49**	**0.06**	**0.13**	0.16	0.13	0.17	0.15	**0.11**
	UJS	0.51	1.29	**0.86**	0.81	0.75	**1.03**	**1.01**	0.17	**0.46**	0.14	0.29	0.76	**0.93**	**1.14**	**0.10**	**0.28**	0.20	0.17	0.22	0.23	**0.31**
Range	VMP	-2.4-2.6	-5.8-5.2	-1.8-2.9	0.1-5.8	-2.0-1.8	-1.6-1.6	-2.0-2.0	-1.2-1.5	-2.9-1.8	-1.7-1.4	0.0-2.9	-1.9-1.9	-1.7-1.5	-2.0-2.0	-0.9-1.2	-0.9-1.2	-0.8-1.3	0.0-1.8	-0.7-3.1	-0.6-1.0	-0.5-0.5
	UJS	-2.7-3.1	-6.2-8.9	-2.2-6.6	0.1-10.7	-3.9-10.7	-3.6-4.5	-7.0-2.8	-4.4-2.8	-4.0-4.8	-2.3-2.3	0.0-5.6	-4.0-4.1	-4.7-4.1	-4.5-4.4	-0.7-0.9	-3.1-3.1	-1.4-0.8	0.1-3.2	-1.4-3.1	-4.7-1.5	-2.0-4.0

Table 2. Results of the positioning study

Abbreviations: Lat = lateral; Long = longitudinal ; UJS = upper jaw support; VMP = vacuum mouth piece.

For the bold numbers, there is a statistically significant difference between the VMP and the UJS.

In general, the ranges for almost all VMP parameters were much smaller than for the corresponding UJS parameters.
The cumulative distribution of the displacement vector length was narrower for the VMP than for the UJS, for all three groups of data (Fig. 6). In particular the tail was much smaller, indicating that the number of outliers and the size of the deviation were much smaller. This is in accordance with the smaller range.

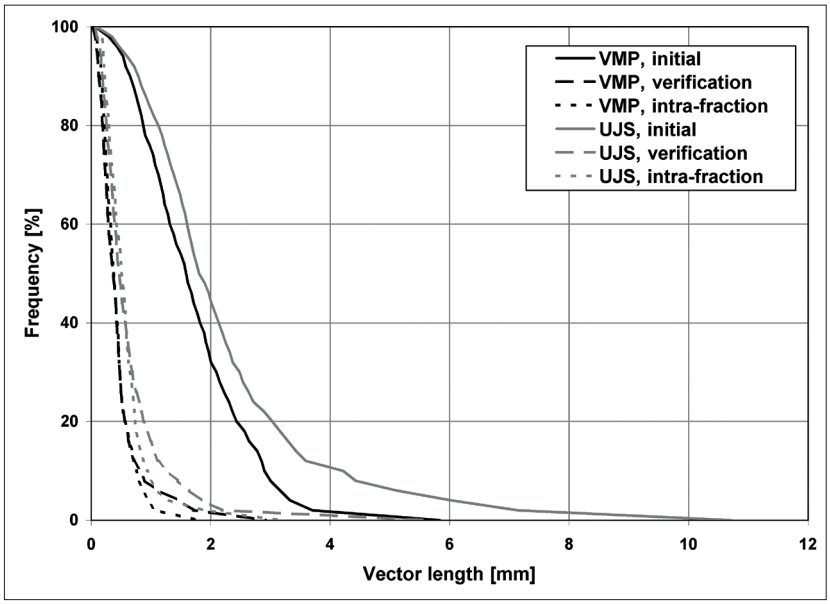

Figure 6. Cumulative distribution of the displacement vector length.

DISCUSSION

The analysis shows that the use of the Exactrac system greatly improved patient positioning accuracy, compared with positioning using the target positioner box. Translational errors were much smaller after Exactrac-based correction. Rotational accuracy was not affected.
The results also show that the VMP significantly improved patient positioning, especially with respect to rotations. The initial positioning accuracy as well as the verification positioning accuracy and the intrafraction stability were increased.
Rotations cannot easily be solved without a 6–degree of freedom couch such as the Robotic Table Top [11]; therefore the improvement observed for the VMP, both for the initial rotations and for the intrafraction rotations, will be useful. The significance of rotations for fairly spherical brain metastases will be very small (especially if cones are used). However for irregular target shapes such as those seen, for example, for meningiomas, often with adjacent critical structures such as the optic nerves, rotations can be significant, although this remains to be proved dosimetrically.
Even when a Robotic Table Top would be used, an advantage of the VMP is the improved intrafraction immobilization. Another advantage is that the range of rotations is limited with the use of the VMP: no rotations were observed that were greater than 3° (which is the practical limit for Robotic Table Top corrections), as opposed to the values noted with UJS used.
The accuracies found in the present study were of the same order of magnitude as the accuracy of the Exactrac system, which we found to be better than 0.5 mm and 0.5°. This may

result in an overestimation of the deviations.

Several studies have been published on positional accuracy for stereotactic treatment, mostly on relocatable fixation systems.

The VMP in the present study originates from the Headfix system [5]. Sweeney *et al.* found three-dimensional (3D) vector lengths of on average 1.9 mm (SD, 1.2 mm). These values can be compared with the VMP results for average and σ for the initial positioning deviations of 1.7 mm and 0.7 mm. This suggests that our results were slightly better, probably because of the addition of the mask. Olch *et al.* [12] reported values similar to those of Sweeney *et al.*

Compared with the results of Baumert *et al.* [6], our results for average vector length after initial positioning seem slightly better both for the upper jaw support and for their bite block compared with our VMP. In part this might be caused by the image registration on CT, which has limited accuracy because of the relatively large slice distance of 2 or 3 mm. The VMP accuracy might also be better because of the vacuum, which Baumert *et al.* did not use.

In the study of Engelsman *et al.* [4], several immobilization devices were compared, among others a mask with or without bite block. The interfraction variability in this study was 3 mm in vector length, either with or without bite block, which was considerably less accurate than for both the UJS and VMP systems after initial positioning. These investigators observed a v_{95} (the vector length that was not exceeded in 95% of the cases) of 6.5 mm. In our study, the v_{95} for the VMP and the UJS were 3.2 and 5.5 mm respectively. This is one of the few other studies in which intrafraction variability is investigated. Engelsman *et al.* found for the mask an average vector length of 1.3 mm and a v_{95} of 3 mm, either with or without the bite block. For the VMP and UJS in our study, we found an average vector length of 0.4 and 0.6 mm and a v_{95} of 0.9 and 1.1 mm respectively. Engelsman *et al.* also found, in agreement with the present study, that the largest deviations were seen in the longitudinal direction.

Another study in which intrafraction variability was measured was from Kim *et al.* [13]. They used infrared reflective markers, fixed to a bite tray, for this. Their fixation method was a three-point mask. This resulted in a v_{95} of 1.5 mm, compared with our values of 0.9 and 1.1 mm for VMP and UJS, respectively. Therefore use of the mask system with either VMP or UJS seems to improve intrafraction stability.

Rosenthal *et al.* [14] investigated inter- and intrafraction accuracy for a two-point mask system either with or without bite block. They looked at both translations (vector length average and SD) and rotations (SD). Their interfraction translations for the bite block system were slightly larger than ours (after initial positioning), whereas their rotations were comparable. Intrafraction motion was much smaller using the bite block and is comparable to ours.

Compared with other published studies on relocatable fixation methods, we see that our system with the VMP gave results either comparable to or better than most other systems, both for inter- and intrafraction positioning.

The positioning results after correction, measured on the verification images, were very good. We can compare these results to the few studies that have been published on accuracy with invasive frames.

Yeung *et al.* [2] measured positioning accuracy using a geometric test phantom. By analyzing portal films, they found a treatment setup error of 0.73 ± 0.23 mm (average vector length ± 1 SD), which was comparable to the 0.7 ± 0.6 mm that we found for the UJS but considerably larger than the 0.4 ± 0.5 mm for the VMP.

Chang *et al.* [15] evaluated the accuracy of cone beam CT registration for radiosurgery and found an average vector length of 1.3 mm for overall accuracy.

Another invasive fixation method is the Talon frame [16]. In this system two screws are inserted in the patient's skull. These are later fixed to a so-called Nomogrip that is attached to the treatment table. This results in an average vector length of 1.4 ± 0.5 mm, which is again larger than our VMP result. The rotations observed (average, 0.2–0.5°) appear to be smaller than with the VMP.

CONCLUSION

To summarize, based on our study results, use of theVMP results in better patient fixation and smaller rotations than the UJS, making it a useful addition to the Mask System. Combined with positioning correction using the X-ray Exactrac system, it is a convenient and accurate alternative to invasive fixation methods.

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CHAPTER 3

Outcome after SRT
of brain metastases

3a: RELATIONSHIP BETWEEN VOLUME, DOSE AND LOCAL CONTROL IN STEREOTACTIC RADIOSURGERY OF BRAIN METASTASIS

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ABSTRACT

The aim of this study is to analyse the efficacy of linear accelerator stereotactic radiosurgery (SRS) on prognostic factors, local control rate and survival in patients with brain metastasis. Patients with either a single metastasis or up to 4 multiple brain metastases with a maximum tumour diameter of 40 mm for each tumour and a Karnofsky Performance Status (KPS) ≥70 were eligible for SRS. SRS was applied to 150 lesions in 86 consecutive patients with a median age of 60 years (median 1 and mean 1.7 lesions per patient, mean KPS 86). Median overall survival was 6.2 months after SRS and 9.7 months from diagnosis of brain metastasis. Multivariate analysis revealed that a KPS of 90 or more ($p = 0.009$) and female sex ($p = 0.003$) were associated with a longer survival. Radiation dose ≤15 Gy ($p = 0.017$) and KPS <90 ($p = 0.013$) were independent predictors of a shorter time to local failure. Five patients showed evidence of radionecrosis with a median survival of 14.8 months. Addition of WBRT neither led to improvement of survival nor to improvement of local control. Improved local control following SRS for brain metastases was associated with KPS ≥90, a radiation dose >15 Gy and a PTV <13 cc. The potential of hypofractionated stereotactic radiotherapy (SRT) for brain metastases of larger volume warrants further study.

INTRODUCTION

Brain metastases develop in 20–40% of cancer patients [1]. Although the prognosis is poor, there is a subgroup of patients who may have improved survival depending on prognostic factors and the treatment applied [2, 3]. The outcome is more favourable in younger patients (<65 years), with a single metastasis, a controlled primary tumour, a Karnofsky performance status (KPS) ≥70 and without any extracranial disease, which combined factors permit a median survival of 13.5 months [4]. Current treatment options include neurosurgical resection, whole-brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), chemotherapy, or a combination of these.

The choice of one modality over the other depends on the presence of prognostic factors related to both patient and tumour characteristics [5, 6]. Nowadays, SRS has probably become the most established modality for treating brain metastasis. SRS is achieved by administering a relatively large, single dose fraction to precisely-defined targets using multiple convergent beams. The purpose of this retrospective study is to present our experience and results with linear accelerator stereotactic radiosurgery for the treatment of cerebral metastases.

PATIENTS AND METHODS

A retrospective analysis of 86 consecutive patients with brain metastases treated with Novalis shaped beam radiation between July 2004 and January 2007 was performed. The general indications for SRS at our institute are: (1) a single brain metastasis or up to 4 multiple brain metastases; (2) maximal diameter of 40 mm or less for each metastasis; (3) KPS of 70 or higher; (4) contra-indications for surgery because of location of tumour in deep or eloquent regions. Radiosurgical treatments were performed on an out-patient base with a Novalis machine (Brain LAB AG, Helmstetten, Germany) at the Department of Radiation Oncology of the Medical Center The Hague (MCH). Referring physicians included neurosurgeons, neurologists and medical oncologists, both from MCH and other institutes. KPS was scored prospectively and patients were retrospectively classified into Recursive Partition Analysis (RPA) class I, II or III [7]. The clinical target volume (CTV) was defined as the gross tumour volume (GTV) without margin. The planning target volume (PTV) of all metastases was formed by expanding the CTV with 2 mm. All patients were treated using a dynamic arc technique, planned with Brainscan 5.31 (BrainLAB AG Helmstetten Germany).

Doses were planned according to volume. Tumours with PTV <8 cc received 21 Gy, tumours with PTV of 8-13 cc had 18 Gy and tumours with PTV >13 cc received 15 Gy. Following SRS, patients received oral dexamethasone (16 mg) for 7 days, which was subsequently discontinued or gradually tapered down in case of longlasting prior use. Patients were seen every 3 months at the radiotherapy clinic and frequently at the neurooncology clinic as well. Follow-up MR scans were made at 3 months after the procedure and every 3 months thereafter. MR scans at baseline and follow-up were reviewed by one of the authors (R.M.) and tumour diameters were measured in 2 dimensions. Tumour response to treatment was classified according to the Macdonald's 2D criteria, [8] i.e., complete response (CR), complete disappearance of tumour; partial response (PR), at least 50% decrease in tumour size (the product of the two largest perpendicular diameters), progressive disease (PD), at least 25% increase in tumour size and stable disease (SD), neither PR nor PD. FDG-PET scans were performed for differentiation between radiotherapy-induced necrosis and tumour progression. For all patients, the date of the last follow-up or of death was retrieved.

Statistical analysis was performed using SPSS 15.0 (SPSS Inc., Chicago, Illinois, U.S.A.). Overall survival and local control curves were calculated with the Kaplan-Meier method. Univariate analyses, using the log-rank test, and stepwise forward conditional multivariate analyses were performed with the Cox regression model to calculate the prognostic value of

Patient		
Number of patients (n)		86
Number of metastases (n)	Solitary	44 (51%)
	Multiple	42 (49%)
Sex (n)	Male	40 (47%)
	Female	46 (53%)
Age (years)	Median	60
	range	33-87
KPS (n)	50	1 (1%)
	60	2 (2%)
	70	11 (13%)
	80	20 (23%)
	90	32 (37%)
	100	20 (23%)
RPA class (n)	I	24 (28%)
	II	59 (69%)
	III	3 (4%)
Primary tumour (n)	Lung cancer	49 (57%)
	Breast	16 (19%)
	Melanoma	11 (13%)
	Colorectal	5 (6%)
	Unknown origin	2 (2%)
	Other	2 (2%)
Extracranial disease (n)	Controlled	44 (51%)
	Progressive	42 (49%)
Presenting symptoms (n)	Focal and cognitive deficits	59
	Seizures	12
	Headache	8
	Asymptomatic	7
Radiosurgically treated metastases		
Location of lesions (n)	Only supratentorial	51
	At least one infratentorial	35
Maximum tumour diameter in horizontal plane (mm)	Median	19
	Range	0.3-5.8
Number of lesions (n)	Total	150
	Mean per patient	1.7
Treatment		
Dose (Gy)	Median	21
	Range	12-25
Total PTV per patient (cc)	Median	13.0
	Range	0.76–72.18
PTV per tumour (cc)	Median	5.1
	Range	0.22-72.18
Chemotherapy (n)		47
WBRT (n)	Before SRS (as treatment)	10
	Before SRS (prophylactic)	1
	In combination with SRS	13
	After SRS (if progression)	12
Neurosurgery (n)	Resection before SRS	5
	Resection after SRS (local progression)	2
	Drain	1
	Stereotactic biopsy	2

Table 1. Patient, tumour and treatment characteristics.

different variables related to survival and local tumour control. For multivariate analysis, those variables with p <0.15 in the univariate analysis were used.

RESULTS

PATIENT, TUMOUR AND TREATMENT CHARACTERISTICS

Eighty-six consecutive patients were analysed. At the time of analysis, 71 patients had deceased and 15 (17%) survived. Patient, tumour and treatment characteristics are shown in Table I. Forty-four patients had a solitary metastasis and 42 patients had multiple metastases. Overall 150 metastatic lesions were treated radiosurgically (median per patient 1, mean 1.7, range 1–4). Patient age ranged from 33 to 87 years with a median of 60 years. Forty-six (46%) patients were female and 40 patients were male. KPS, prospectively scored prior to SRS, was median 90 (mean 86, range 50-100). Twenty-four patients (28%) belonged to RPA class I, 59 patients (69%) to RPA class II and 3 patients (4%) to RPA class III.

Forty-six patients (55%) came in with motor-, speech,- brainstem- or cerebellar dysfunction, a minority had seizures without focal deficit (14%) or had a headache (9%), cognitive deficits (10%) or visual signs (5%). Seven (7) patients were asymptomatic (8%). Twenty-one (21) patients (24%) had brain metastasis as presenting symptom of their primary disease. In 35 patients (41%) there were one or more infratentorial metastases with or without supratentorial metastasis. Lung cancer, breast cancer and melanoma were the most common primary tumours.

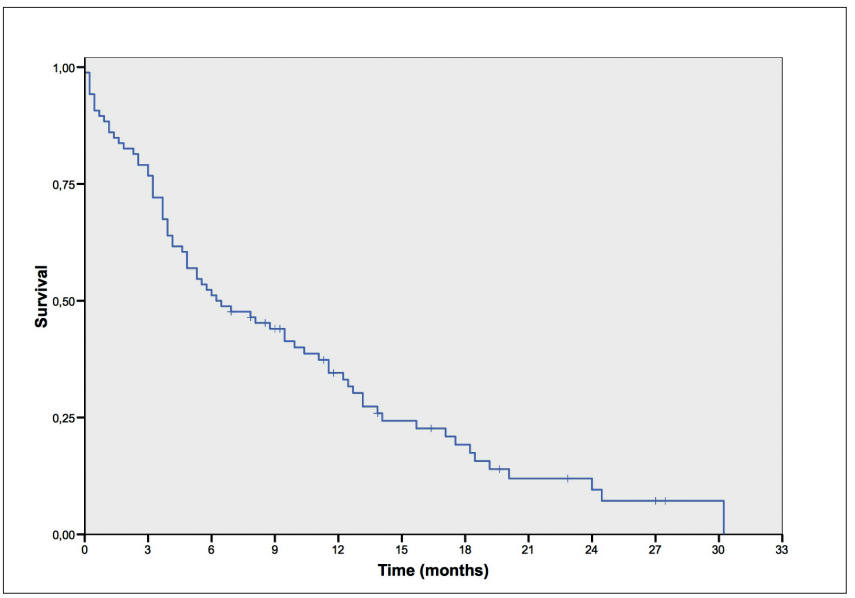

Figure 1. Kaplan-Meier overall survival curve.

Seventy-four patients had SRS as primary treatment of cerebral metastasis, of whom 13 (15%) received SRS in combination with WBRT, mainly relatively young patients (<65 years) with good performance and without any extracranial progression. Twelve patients received SRS as salvage therapy because of recurrence after initial WBRT (7 patients), initial neurosurgical resection (2 patients) or both (3 patients). One patient had had prior prophylactic WBRT as part of his treatment for small-cell lung cancer.

Doses ranged from 12 Gray (Gy) to 25 Gy (median 21 Gy), all specified to the 80% isodose line. Median total PTV of all metastases was 13.0 cc (range 0.76–72.2). Median follow-up

was 6.3 months (mean 8.5, range 0.1–30.2), median follow-up of survivors was 12.9 months (range 6.9 - 27.5 months). Twenty-four patients, harbouring 44 metastases (29%), died before a first follow-up scan at 3 months could be scheduled and 11 other patients never had a follow-up scan due to other reasons, resulting in 51 patients with 90 metastases (60%) with at least one available follow-up MRI, allowing calculation of local control rates. MR scans at 3 months and 6 months were available in 78% and 61% of surviving patients.

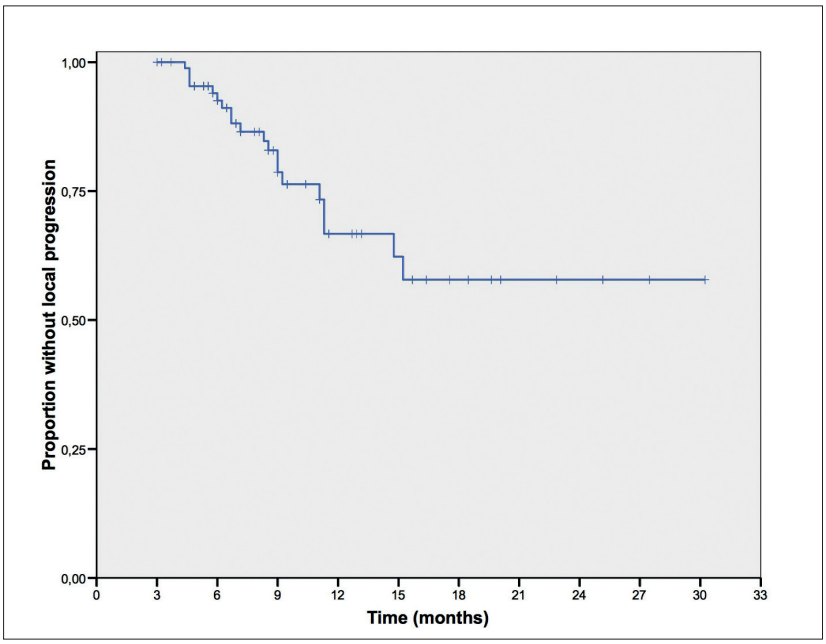

Figure 2. Kaplan-Meier local tumour control curve.

SURVIVAL AND LOCAL CONTROL

Median survival from time of diagnosis of cerebral metastasis was 9.7 months, and median overall survival after SRS (Figure 1) 6.2 months (95% CI 3.0–9.4 months, mean 10.1, range 0.1–30.2). Actuarial survival rates after SRS were 77% at 3 months, 53% at 6 months, 35% at 1 year and 12% at 2 years. Survival of RPA classes I, II and III was 6.9 months, 6.0 months and 4.6 months, respectively. A complete response (CR) was achieved in 11 metastases (12%), partial response (PR) in 48 metastases (53%) and stable disease (SD) in 29 metastases (31%), resulting in a short-term local control rate of 94%, which was maintained at the last MR follow-up for 70 of 90 (78%) evaluable lesions.

The actuarial rates without local progression after SRS were 82%, 63% and 57% at 6, 12 and 24 months respectively. Figure 2 shows the local tumour control curve. We did not observe early progression of a lesion due to tumour growth within 3 months. One lesion (1%) probably progressed within 3 months due to radionecrosis. Delayed tumour progression was noted in 20 tumours (22%):in 9 lesions after previous CR or PR, in 9 lesions after SD, in 1 lesion after a prior radionecrotic reaction and in 1 lesion at 7 months when only the first radiographic follow-up was made. The median time to progression of a metastasis was 7.8 months (mean 8.3, range 4–15 months).

Five tumours (6%) showed signs of radionecrosis based on MR and FDG-PET scanning after a median of 5.8 months (mean 5.4, range 2.5–7.4) In four patients, these lesions were asymptomatic, but led to progressive symptoms in one patient despite administration of

steroids, after which it was successfully resected and did not recur for over 2 years. Histopathological examination confirmed radionecrosis. We did not observe any clear relationship between radionecrosis and prior or additional WBRT (3 patients without WBRT and 2 patients with earlier WBRT had radionecrosis), dose of radiation, PTV or the histopathology of the tumour. Median survival after a radiological diagnosis of radionecrosis in these 5 patients was 14.8 months.

Variable		Median survival		Median survival	Univariate p-value	Multivariate p-value
Sex **	Female	11.1	Male	4.2	0.014	0.003
Age	<65	8.1	≥65	4.2	NS	NS
KPS **	≥90	9.5	<90	3.9	0.016	0.009
Extracranial disease	Controlled	9.9	Progressive	5.8	NS	
RPA	Class I	6.9	Class II	6.0	NS	
Primary tumour	Breast	13.2	Non-breast	5.3	NS	NS
Focal deficits	No focal deficits	8.1	Focal deficits present	6.0	NS	
Infratentorial metastasis	No infratentorial metastases	9.5	Infratentorial metastasis present	4.2	NS	NS
Number of metastases	Solitary	7.6	Multiple	6.0	NS	
Presenting sign of cancer *	No	6.9	Yes	4.8	0.032	NS
Total PTV *	< median (13.16 cc)	9.5	≥ median (13.16 cc)	3.7	0.045	NS
PTV largest lesion *	< median (11.79 cc)	9.5	≥ median (11.79 cc)	4.2	0.041	NS
WBRT	WBRT	9.5	No WBRT	4.2	NS	
SRS as salvage	No salvage	6.2	Salvage	4.8	NS	
Chemotherapy	Chemotherapy	8.1	No chemotherapy	3.9	NS	NS

Table 2. Univariate and multivariate analysis of prognostic factors for survival.
***p <0.05 in univariate analysis. **p <0.05 in multivariate analysis.**

Eighteen patients (35% of patients with follow-up scans) showed new cerebral metastasis (distant progression) at a median of 4.7 months after SRS. Twelve patients (14%) received salvage WBRT either because of this or because of local progression. In 6 patients (7%) SRS was repeated after a median period of 10.6 months (range 2.5–17.8 months). Two of these 6 patients had local progression and 4 had distant cerebral metastasis. Median survival after the second SRS was 7.4 months (range 3.0–11.1 months). Finally, the retrospective analysis of the follow-up visits at the clinic showed that at 3 months' follow-up, 43 patients (i.e., 56% of all patients and 78% of surviving patients) had stable or a better performance status than at the time of SRS. At 6 months follow-up, 58% of surviving patients had a stable clinical condition.

PROGNOSTIC FACTORS

Results of the univariate and multivariate analysis for prognostic factors regarding survival are shown in Table II. Univariate analysis showed improved survival for female sex, KPS ≥90, smaller PTV and cerebral metastasis as presenting sign of primary tumour. RPA classification did not have prognostic value in this series. Patients with breast cancer showed a trend for better survival, although not significantly ($p = 0.119$). We found no difference in survival

between patients who received SRS as primary therapy and patients who received SRS as salvage therapy (median 4.8 vs. 6.2 months, $p = 0.55$). There was a trend for patients >65 years to die within 3 months ($p = 0.057$). Multivariate analysis revealed that female sex and KPS (Figure 3) were independent predictors for survival ($p < 0.05$).
Prognostic value for local control was tested for SRS treatment variables and relevant demographic and tumour variables. Improved local control, analysed in the univariate model, was associated with KPS ≥90, PTV <13 cc and a radiation dose >15 Gy (Table III). The multivariate model revealed that both KPS and radiation dose were independently associated with improved local control ($p < 0.05$). Radiation dose up to 15 Gy resulted in decreased local control ($p = 0.007$) compared to higher doses (Figure 4). The actuarial local progression-free rates at 12 months for doses 12–15 Gy, 18–20 Gy and 21–25 Gy were 37%, 64% and 82% respectively.

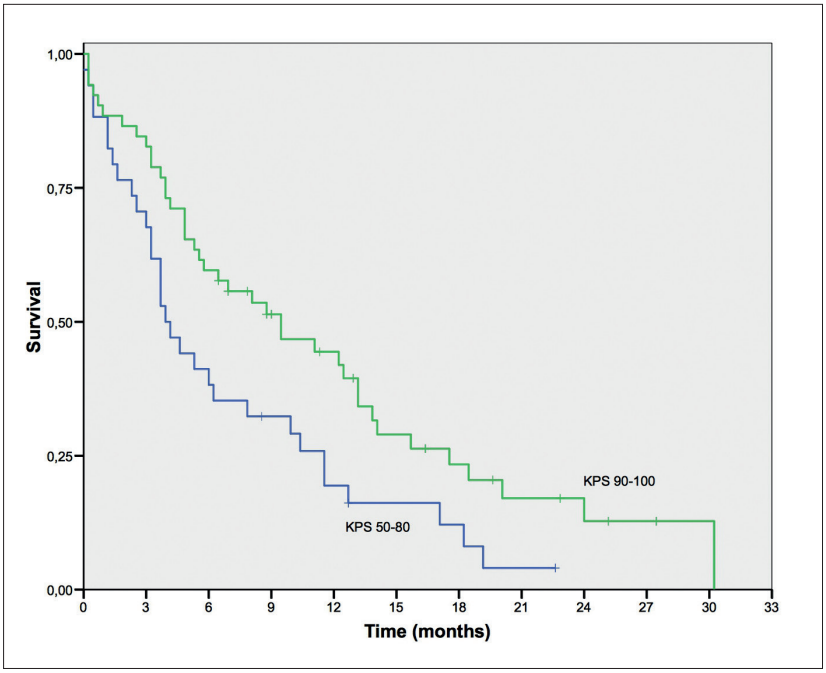

Figure 3. Kaplan-Meier curve for overall survival according to KPS (log rank p = 0.016).

DISCUSSION

We performed a retrospective analysis of 86 consecutive patients who were radiosurgically treated for brain metastases from 2004 to 2007. Both radiosensitive and radioresistant tumours were treated and radiation was administered to the 80% isodose with the amount of dosing based on radiosurgical volume (PTV). The median overall survival in our study was 6.2 months (95% CI 3.0 – 9.4 months) corresponding to earlier reports on results with SRS [9-13]. It is similar to or better than survival after WBRT, which prolongs median survival to 3–6 months [5, 14-17]. KPS proved to be the strongest independent prognostic factor for overall survival followed by female sex, which has been recognized before as a prognostic factor [18].
Possibly due to relatively limited number of patients, we did not assess that RPA classification was significantly prognostic, although the survival of the 3 classes (6.9 months, 6.0 months

and 4.6 months respectively for class I, II en III) matches well with former reports [7, 9-13]. Difficulties in assessing the control of primary tumour with brain metastasis as the presenting sign of the underlying tumour may have contributed to this [19].
Patients who had received both SRS and WBRT showed a similar survival to those who received only SRS. This corresponds to what others have observed, although in some studies, the combination of SRS and WBRT was associated with a better survival in patients with a single brain metastasis [10, 12, 20-23]. A survival advantage could not be observed in a recent randomised trial on 132 patients with brain metastases who received SRS either with or without additional WBRT, although better local control was achieved with additional WBRT [24]. A benefit of omitting additional WBRT as a routine is a lower risk on "radiation-induced dementia" in potential long-term survivors [25, 26].

Variable	Univariate p-value	Multivariate p-value
Sex	NS	
Age	NS	NS
KPS	0.001	0.013
Primary tumour	NS	
PTV	0.042	NS
Dose	0.007	0.017
WBRT	NS	

Table 3. Univariate and multivariate analysis of prognostic factors for local control.

Another advantage is a shorter duration of treatment since WBRT is administered in fractions, usually taking 2 to 4 weeks. One option in case of progression after prior treatment for brain metastasis is application of SRS as salvage treatment. In our series, SRS for recurrent brain metastasis after a prior neurosurgical resection or after WBRT was applied to 12 patients, showing a subsequent similar survival to that with SRS given initially. Also, earlier reports indicate the usefulness of SRS as salvage therapy after previous WBRT [27-29]. Recently a median survival of 7.4 months after a repeated, second SRS was observed for local or distant recurrences of brain metastasis which was comparable to the overall survival after a first SRS [30]. Although our numbers were smaller, we also observed a median survival of 7.4 months after a second SRS in six patients. These data further support the feasibility of repeated SRS for local or distant recurrences in selected patients.
Contrary to many other reports on SRS, we used a strict definition of local progression using Mcdonald's criteria based on MR images [8]. Local control rates in past studies have not been reported in an uniform way [9-12, 20, 21]. In order to provide a better insight, we have chosen to report both short-term local control and local control at the last MR follow-up, together with actuarial Kaplan-Meier rates at 6, 12 and 24 months. Still, in our series 29% had no MR follow-up because of early deaths before a first post-radiosurgical scan could be made. We believe this limits the results of our study as well as the results of other studies on local tumour control.
No author has specifically addressed the problem of local control and early death within 3 months. Retrospectively, it is often difficult to decide whether death has been caused by local brain failure or by systemic progression of cancer. In a separate analysis we did not find any other prognostic factors for death within 3 months than the ones also valid for overall survival, except for a trend associated with older age. Despite difficulties concerning its assess-

ment, our observed local control rate of 94% in the first months after SRS and 78% on the last available radiographic follow-up corresponds to earlier reports [13].
The analysis of prognostic factors for local control revealed that the tumours that had received a larger radiation dose than 15 Gy showed a better local control. Although doses less than 18 Gy were mainly given to large tumours with a large PTV (81% of tumours that received 12–15 Gy had a PTV of ≥13 cc), local control was independent of PTV in the multivariate analysis. So far, only limited data are available concerning the optimal radiation dose. From a retrospective analysis of 162 radiosurgically treated lesions, Matsuo *et al.* recommended treating tumour volumes of 10-15 cc with 20 Gy and volumes less than 10 cc with 25 Gy [31].
A prospective study on 31 brain metastases receiving SRS dose of 10 Gy plus WBRT showed less favourable results (one year local control rate 61%) than previous studies using SRS with doses of 15–16 Gy [32]. In another series, local control depended on radiation doses, i.e., ≥18 Gy was superior to 15–17 Gy and the latter being superior to <15 GY, and in another study doses >14 Gy were superior to 11–14 Gy [33, 34]. In one RTOG study (trial 90-05), the maximum tolerable dose of single fraction SRS was 24 Gy for tumours ≤20 mm, 18 Gy for 21–30 mm and 15 Gy for 31–40 mm [35]. Unacceptable CNS toxicity was more frequent in larger tumours. A series from Cleveland where 436 patients were treated according to the same dosing scheme, observed that a dose of 24 Gy showed a lower risk on local progression than doses of 15 or 18 Gy [36]. Dose-diameter relations in our study were comparable to these studies, as all large lesions (>30 mm) received ≤15 Gy.

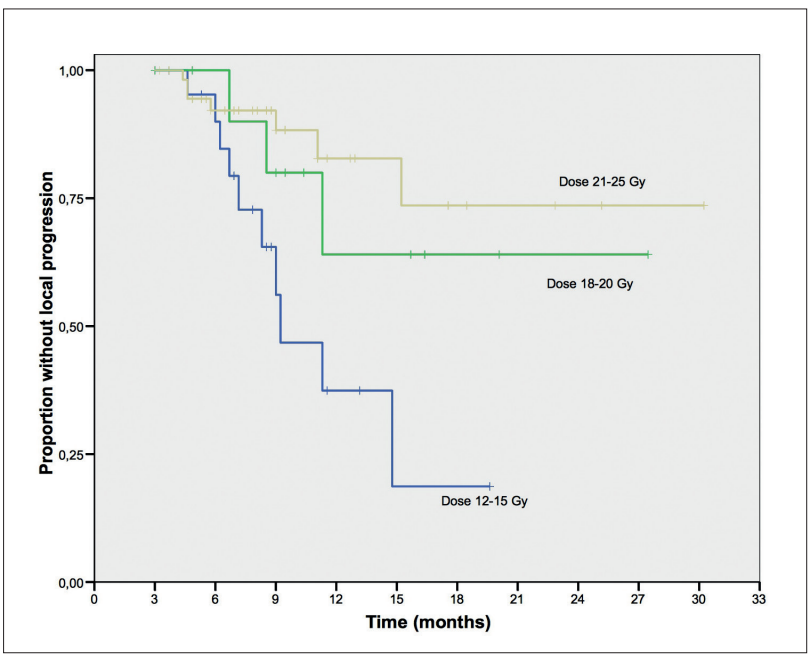

Figure 4. Kaplan-Meier local tumour control curves for different radiation doses (log rank p = 0.007).

Since more failures of local control were seen with smaller doses of ≤15 Gy mainly given to larger volumes, one could argue that these tumours could better be neurosurgically resected as a higher radiation dose may lead to unacceptable toxicity [35]. Another strategy is the use of hypofractionated stereotactic radiotherapy (HSRT), which allows for a higher total dose. This is mainly applied to tumours not suitable for single fraction SRS, either because of

location or size of the lesion or because of progressive intracranial disease [37-41]. Dosing schemes used in these studies were 3 x 9 Gy, 4 x 8 or 9 Gy and 5 x 6 to 8 Gy, and these show that HSRT is feasible, safe and effective. Recently, a better survival with hypofractionated SRT compared to single fraction SRT was seen [42], although the median survival of single fraction SRS in this study was clearly shorter (16 weeks) compared to many other previously published series [9-13].

Radionecrosis was documented by MRI and FDG-PET in 6% of our irradiated brain lesions. In earlier series, a frequency of radionecrosis was seen in 1–10% of cases after SRS [9, 18, 21, 35, 43, 44], and 25% in one series with tumour diameters of more than 40 mm [45]. Also in the RTOG 90-05 trial the most important predictor for radionecrosis was tumour size, other risk factors were higher radiation dose, prior radiation treatment (both WBRT and SRS) and the size of erroneously irradiated normal brain tissue [9, 35, 46, 47].

When patients have progressive symptoms of mass effect of radionecrosis, first line therapy can consist of high-dose steroids and second line therapy offers the options of either surgery or hyperbaric oxygen [48, 49]. In our series, one patient had progressive symptoms despite treatment with steroids for a radionecrotic lesion, that was subsequently successfully resected, after which the patient was symptom-free for over 2 years. Radionecrosis in five patients appeared at median 5.8 months after SRS with a median overall survival after SRS of 17.5 months. However, this long survival can also be seen as a consequence of bias since a long period of survival can be considered an essential condition for developing radionecrosis in the brain parenchyma.

Percentages of up to 25% have indeed been reported in long-term survivors (>2 years) after SRS [50]. Thus, rather than considering it just as a side-effect, radionecrosis after SRS on radiographic follow-up can perhaps be seen as a favourable prognostic factor and, if symptomatic, can often be dealt with successfully.

In conclusion, survival and local control after SRS for cerebral metastases in our series were comparable to previous reports, and did not show untoward effects. Performance status was the main prognostic factor for survival, and the dose of radiation was crucial for the achievement of local control. The addition of WBRT to SRS had neither a beneficial effect on survival nor on local or distant tumour progression. In our series, application of salvage SRS, either after neurosurgery or WBRT or as repeated SRS, contributed to clearly improved survival rates in selected patients.

Occurrence of radionecrosis was mainly asymptomatic, and survival in patients with radionecrosis was better than survival of the whole group of patients. Brain metastases with a large PTV were difficult to control by single fraction SRS in doses of ≤15 Gy. For lesions larger than 13 cm^3 – apart from considering surgery for accessible lesions – the merits of hypofractionated SRT warrant further study.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the study.

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3b: DOSE–EFFECT RELATION IN STEREOTACTIC RADIOTHERAPY FOR BRAIN METASTASES. A SYSTEMATIC REVIEW

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ABSTRACT

Purpose: Stereotactic radiotherapy (SRT) of brain metastases is considered effective when long-term local control is obtained. However, dose–effect data are scarce. We, therefore, performed a systematic literature search to assess the evidence concerning the relation of SRT dose and local control probability.

Methods and materials: A search was performed for papers describing patients treated with SRT for brain metastases, published from 1990 through 2009, in the electronic databases Medline (Pubmed) and Embase. We selected only papers reporting actuarial local control probability, in which a fixed dose had been pre-scribed and in which the size of the metastases was given. Series with SRT as a boost after whole brain irradiation (WBI) or with SRT after surgery were excluded. From the selected papers we extracted data on dose, local control rates and necrosis rates. Biological effective doses of the linear-quadratic-cubic model, using an α/β of 12 Gy (BED_{12}), were calculated and a dose–response curve was constructed.

Results: Eleven papers fulfilled the selection criteria for further analysis. Six-month local control rates were higher than 80% in almost all the series irrespective of dose. Twelve-month local control rates, however, varied and were higher than 80%, higher than 60% and lower than 50% with single doses of ≥21 Gy, ≥18 Gy and ≤15 Gy, respectively, and 70% or higher with fractionated SRT (FSRT). A BED_{12} of at least 40 Gy was associated with a twelve–month local control rate of 70% or more.

Conclusion: Local control after single fraction SRT is highly dependent upon dose and is high (>80%) after 21 Gy or more, but low (<50%) after 15 Gy or less. We conclude that SRT for brain metastases should preferably be applied with a BED_{12} of at least 40 Gy corresponding with a single fraction of 20 Gy, two fractions of 11.6 Gy or three fractions of 8.5 Gy.

Brain metastases occur in 20–40% of patients with cancer [1]. The incidence of symptomatic brain metastases seems to be increasing as more effective systemic treatments have become available [2]. The prognosis of patients with brain metastases remains poor, despite the developments in modern treatment techniques [3]. Patients with brain metastases were originally divided into three prognostic subgroups using the recursive partitioning analysis published by Gaspar *et al.*, but recently it was shown that prognostic factors vary by primary diagnosis [4,5]. Stereotactic radiotherapy (SRT) is one of the accepted treatment modalities for brain metastases, but there is still a debate if and when whole brain irradiation (WBI) should be combined with SRT [6]. SRT plus WBI is associated with improved local tumor con trol and neurological functioning compared to either treatment alone, but only in subgroups of patients this results in improved survival [3,7–9]. However, patients treated with SRT and WBI are at a greater risk of neurocognitive decline than patients treated with SRT alone [10]. Local control rates are probably higher with the addition of WBI as a result of the higher total radiation dose when both modalities are combined.

The primary goal of SRT is a long lasting local control, as most local recurrences are symptomatic and associated with neurological deficits [11]. Local control rates are also reported to improve with higher minimum SRT doses [7,12–16]. Increasing SRT doses may not only lead to higher local control rates, but also to higher rates of radiation necrosis [17]. A correlation has been demonstrated between target size and risk of necrosis [17]. However, the diagnosis of radiation necrosis is difficult and toxicity-risk predictions cannot be made [18,19]. As the radiation necrosis rate is determined by the dose in relation to the size of the tumor, it is a common practice to administer higher SRT doses to smaller tumors and vice versa.

However, there is no consensus about the optimal SRT doses. We, therefore, performed a systematic literature review to collect data on local control rates of brain metastases with SRT. The purpose was to summarize the currently available evidence concerning the relation between SRT dose and local control and to define radiation schemes with a twelve-month local control rate of 70% or higher.

MATERIALS AND METHODS

We performed a search for all articles about SRT of brain metastases in the electronic databases Medline (Pubmed) and Embase. We only included papers in English, Dutch, German or French describing patient series published in peer-reviewed journals from 1990 through 2009.

SELECTION OF RELEVANT RESEARCH

We used a selection process in two steps to find the appropriate papers. In the first step we selected only those papers that reported actuarial local control rates of the irradiated brain metastases. A second selection step was done to find the papers in which actuarial local control rates could be related to radiation dose. Therefore, we selected, from the remaining papers, those series in which a fixed dose had been prescribed either to all treated metastases or to clearly defined groups of metastases (with local control data in these groups). Furthermore, at least 10 patients had to be included, who had received SRT as primary treatment or SRT for recurrence after whole brain irradiation (WBI), but not SRT as boost after surgery. Series in which all patients had a planned SRT boost after WBI were excluded in this second step. The papers that remained after the second selection step form the basis of this study.

ANALYSIS OF THE SELECTED PAPERS

From the remaining papers the following data were retrieved: number of patients and number of metastases treated, percentage of patients that received or had received WBI, dose prescription, given minimum dose related to tumor diameter or volume, treatment machine

and technique, six and twelve months local control rates, twelve months survival rate and radiation necrosis rate.
For this analysis we had to use the local control rates as reported in the papers. We could not correct for the relatively small differences in the definition of local control between the papers. Local control was defined as absence of any increase in size, absence of significant increase in size or no increase of at least 25% in size. It was not always clearly stated if increase in size due to suspected radiation necrosis was considered a failure or not.

Author	N patients	N metastases	Diagnoses	Range of diameters/ volumes[b]	Dose/ specifation isodose	GTV-PTV margin (mm)	% WBI[a] (patients)	RTx Machine	Technique
Matsuo (1999)[31]	92	162	All histologies	<3 cm/ <10 cm^3	1x25 Gy/50%	0	0%	Lineac	Circular arc
Chang (2003)[25]	135	153	All histologies	<2 cm/ <5 cm^3	20-24 Gy/70-100%	0	13%	Lineac	Circular arc
Lutterbach (2003)[30]	101	155	All histologies	<3 cm	18 Gy/80%	0-2	0%	Lineac	Circular arc
Chang (2005)[26]	189	264	Melanoma, sarcoma, renal cell carcinoma	<4 cm/ 27.5 cm^3	RTOG/60-100%	0	8%	Lineac	Circular arc
Ernst- Stecken (2006)[28]	51	72	All histologies	1-5 cm/ 0.3-65.6 cm^3	5x7 Gy/90% or WBI+ 5x6 Gy/90%	3	57%	Novalis	Conformal beam/ Dynamic arc
Vogelbaum (2006)[34]	202	375	All histologies	<4.5 cm	RTOG/50%	0	76%	GK	GK
Narayana (2007)[32]	20	20	All histologies	2-5 cm/	5x6 Gy/100%	3	0%	Lineac	IMRT
Chao (2008)[27]	111	?	All histologies	<4 cm	RTOG/?	0	0%	GK	GK
Higuchi (2009)[29]	43	46	All histologies	3-4.5 cm/ 10-36 cm^3	3x10 Gy/50%	0	0%	GK	GK
Molenaar (2009)[36]	86	150	All histologies	<4 cm	RTOG/80%	2	15%	Novalis	Dynamic arc
Saitoh (2009)[33]	49	78	Non small cell lung cancer	<4 cm	3x13 Gy/90% or 3x14 Gy/90%	3	0%	Lineac	Conformal beam

Table 1. Patients and treatments reported in the 11 selected papers.
GK: Gamma Knife
RTOG: dosage scheme from RTOG 90-05: tumors with a diameter of 0-2 cm, 2-3 cm and >3 cm receive 1x20-24 Gy, 1x18 Gy and 1x15 Gy respectively.
[a] Percentage of the patients who received SRT additional to WBI. Patients who received WBI as primary treatment with salvage SRT or WBI as salvage after SRT are not counted in this column.
[b] For comparison diameters are estimated if only volumes are mentioned in the paper.

We considered the minimum dose in the planning target volume (PTV) as the given dose. In some papers the PTV was equal to the gross tumor volume (GTV), but in others a GTV–PTV margin was used, usually not more than 2 mm. We did not attempt to correct for these differences, although there is an influence on the actual dose in the GTV.
It was also not possible to correct for differences in dose specification, although the biological effect of these differences may not be negligible. Finally, we also decided not to take into account the timing of WBI, as there was not always sufficient information in the papers, to decide whether the SRT and WBI were a combined treatment, or SRT or WBI was used as salvage treatment.
To compare the different treatment schemes described in the selected articles, biological effective doses (BEDs) were calculated using the adjusted linear-quadratic BED (LQ-BED) concept. In general, the occurrence of a biological effect E depends on the dose in a linear

and quadratic fashion: $E = n(\alpha d + \beta d^2)$ with n being the number of fractions, d being the dose per fraction, and α and β being parameters that determine the initial slope and curvature of the underlying cell-survival curve. From this equation, the BED can be calculated as: $BED = nd [1 + d/(\alpha/\beta)]$ [20,21]. However, this model describes the responses to ionizing radiation very well at doses upto about 18 Gy [22]. At higher doses the underlying survival curve is found to more closely resemble a linear relationship between survival and dose. Adjusting the LQ-model to account for the more linear response at higher doses can be done by adding an additional term proportional to the cube of the dose. In this so-called LQC model $E = n(\alpha d + \beta d^2 - \gamma d^3)$ and $BED = nd [1 + d/(\alpha/\beta) - d^2/(\alpha/\gamma)]$ [23]. Joiner showed that the survival curve becomes straightened at dose D_1 by choosing $\gamma = b/(3D_1)$, in his example the LQC curve becomes a straight line at a dose of 18 Gy [23].

Author	Diameter (cm)	Dose (Gy)	BED_{12} (Gy)	6 month local control (%)	12 month local control (%)	12 month survival (%)	Radiation necrosis rate (%)
Matsuo (1999) [31]	0-3	25	[b]53.0	100	93	40	Na
Chang (2003) [25]	0-2	20-24	41.0-50.7	Na	69	[a]48	[a]1
	0-1	20-24	41.0-50.7	97	86		
	1-2	20-24	41.0-50.7	82	56		
Lutterbach (2003) [30]	0-3	18	[b]36.0	93	91	27	1
Chang (2005) [26]	1-3	15-18	28.6-36.0	Na	38	31	3
Vogelbaum (2006) [34]	0-2	24	[b]50.7	92	85	[a]50	Na
	2-3	18	[b]36.0	87	49		
	3-4.5	15	[b]28.6	71	45		
Chao (2008) [27]	0-2	22-24	45.9-50.7	97	92	[a]32	[a]2
	2-4	15-18	28.6-36.0	83	62		
Molenaar (2009) [16]	0-2	21	[b]43.4	100	82	[a]35	[a]6
	2-3	18	[b]36.0	95	65		
	3-4	15	[b]28.6	95	37		

Table 2. Actuarial local control and survival rates and crude radiation necrosis rates from the papers reporting about single fraction SRT.

Na: Not available

[a] data reported for the entire patient cohort

[b] data used in Figure 3

It is widely accepted that α/β is about 10–15 Gy for tumors and acutereacting tissues. We used for the brain metastases the value of 12 Gy (BED_{12}) [24]. Because with SRT high single or high fraction doses were used we applied the LQC model and calculated the BED as $nd[1 + d/(\alpha/\beta) - d^2/(\alpha/\gamma)]$. With α/β = 12 Gy and supposing that the survival curve becomes a straight line at D_1 = 18 Gy, and with $\gamma = \beta/(3D_1)$, $\alpha/\gamma = \alpha/(\beta/(3D_1)) = 648$ Gy^2, the BED_{12} is calculated as: $BED = nd[1 + d/12 - d^2/648]$.

Author	Diameter (cm)	Dose (Gy)	BED_{12} (Gy)	6 month local control (%)	12 month local control (%)	12 month survival (%)	Radiation necrosis rate (%)
Ernst-Stecken (2006) [28]	1-5	5x6-7	43.3-52.8	89	76	Na	Na
Narayana (2007) [32]	2-5	5x6	[b]43.3	90	70	42	Na
Higuchi (2009) [29]	3-4.5	3x10	[b]50.4	90	76	30	0
Saitoh (2009) [33]	0.4-3.8	3x13	[b]71.1	90	89	[a]61	[a]12
		3x14	[b]78.3	100	83		

Table 3. Actuarial local control and survival rates and crude radiation necrosis rates from the papers reporting about fractionated SRT.
Na: Not available
[a] data reported for the entire patient cohort
[b] data used in Figure 3

RESULTS

Using the search strategy we found 260 potentially relevant articles. Actuarial local control after SRT was reported in 123 of these papers. Finally, eleven papers contained data that could be used to relate dose to local control [16,25–34]. Table 1 shows patient and treatment characteristics of the 11 remaining papers used in this study.
From two of these 11 papers only part of the reported results could be used for the final analysis.

Matsuo *et al.* reported about 162 metastases in 92 patients [31]. In this series a group of 51 patients could not be used for the analysis, because they received a wide range of doses (10– 22 Gy) for metastases with a volume upto 33 cm^3. However, the remaining group of 41 patients could be used as they received the fixed dose of 25 Gy for metastases upto 10 cm^3. Chang *et al.* described a series of 189 patients with 264 "radioresistant" brain metastases, treated using the RTOG 90-05 scheme [26]. Local control rates are only reported for metastases receiving upto 20 Gy, split into groups of more or less than 1 cm diameter. As it was reported that the RTOG scheme was used, we could not determine what doses were given to metastases with a diameter less than 1 cm. Consequently we did not use the data of the metastases with a diameter less than 1 cm.

Tables 2 and 3 show the 6- and 12-month local control rates, the 12-month survival rates and the crude radiation necrosis rates with the corresponding tumor diameters and the given doses from the series reporting about single fraction SRT (Table 2) and fractionated stereotactic radiotherapy (FSRT) (Table 3). Six-month local control rates are higher than 80% for all except one single fraction series and higher than 90% for all FSRT series. Twelve-month local control rates vary considerably in the single-fraction series, depending on the dose. Twelve-month local control rates are higher than 80% with doses above 20 Gy and higher than 60% with a dose of 18 Gy. Reported twelve-month local control rates with a dose of 15 Gy are below 50% in all but one series. FSRT series all report twelve-month local control rates higher than 70%. Radiation necrosis rates are not reported consistently. The highest rate (12%) was found after 3x13Gy or 3x14Gy.

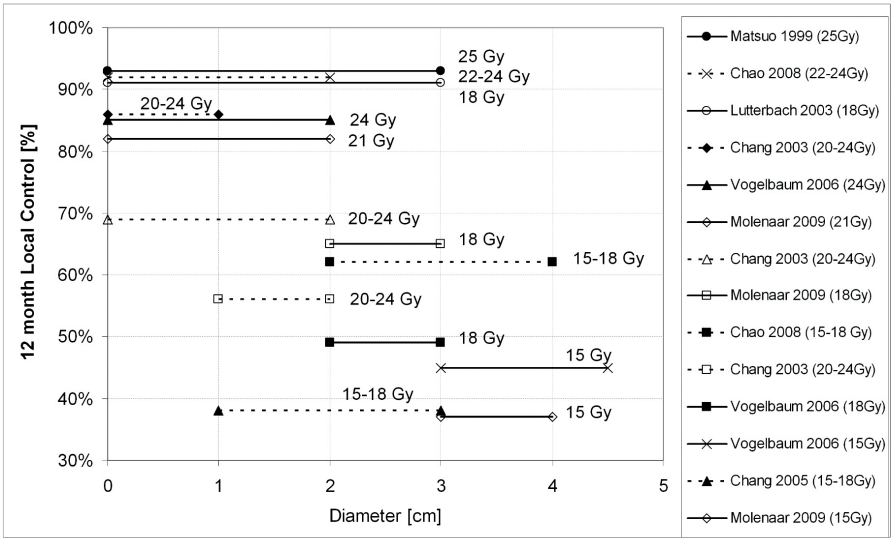

Figure 1. Line plot representing the relation between single fraction SRT, the diameters of the treated metastases and twelve-month local control rates.

We constructed line plots as shown in Figs. 1 and 2 to obtain a better insight into the differences in twelve-month local control rates after all the reported SRT dosage schemes.
Fig. 3 shows the relation between BED_{12} and twelve-month local control rates. From this we concluded that a BED_{12} of at least 40 Gy is needed for a twelve-month local control rate of 70% or more.

DISCUSSION

In this systematic literature search we identified 11 descriptive papers in which actuarial local control rate could be related to applied doses. All studies were characterized by a retrospective design. Six-month local control rates were higher than 80% in almost all series irrespective of dose. Twelve-month local control rates, however, varied substantially and were higher than 80% with a single dose above 20 Gy, higher than 70% with the described FSRT schemes, higher than 60% with a single dose of 18 Gy and almost always below 50% with a single dose of 15 Gy. We found that a BED_{12} of at least 40 Gy was necessary to obtain a twelve-month local control rate of 70% or more.

We could relate the volume of the metastases with the given dose in only 11 of the 123 papers that reported actuarial local control rates. Dose prescription in single fraction SRT is often not based on tumor volume, but on estimated late radiation toxicity rates, resulting in a wide range of dose levels in the majority of papers. Some authors use the so-called integrated logistic formula to prescribe doses and estimate complications [35]. In other series dose prescription is based on RTOG 90-05, a prospective study designed to establish the maximum tolerated dose of single fraction radiosurgery in patients with recurrent previously irradiated brain metastases and primary brain tumors [17]. However the relation between dose and local control in RTOG 90-05 was not reported. The 11 descriptive studies we found contain the best available evidence.

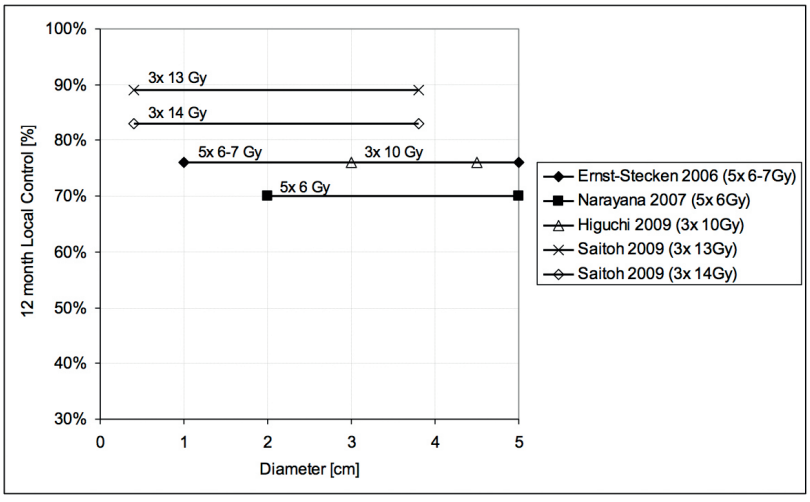

Figure 2. Line plot representing the relation between FSRT dose schedules, the diameters of the treated metastases and 12-month local control rates.

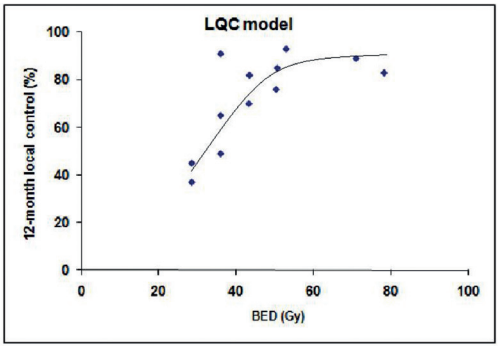

Figure 3. Diagram showing the relation between BED_{12} and 12-month local control rates. Data from papers with a range of doses were not used for this diagram, i.e., used BED_{12} values are indicated with [b] in Tables 2 and 3. A dose–response curve is constructed by eye fitting.

The definition of local control is not uniform, but in most papers the absence of any tumor growth is considered local control. Enlargement of the tumor after SRT can be a true recurrence or radiation necrosis and modern MRI techniques can be helpful to make the distinction [18]. However, these techniques were probably not available or applied in all 11 studies.

This slight uncertainty about the recurrence rates, combined with the observation that radiation necrosis has in none of the papers been reported as actuarial rate but seven times as crude rate and four times not at all, must be considered a weakness of this study.
In most series 30–50% of patients are still alive after 12 months [16,25–27,29–32,34]. As local control for the rest of the patient's life is the treatment goal for SRT, the 12-months local control rate can be considered as a measure of the effectiveness of a treatment scheme. To our opinion the 12-month local control rate should be at least 50%, but preferably more than 70% to state that the treatment is sufficiently effective. Higher local control rates should be weighed against the disadvantage of higher radiation necrosis rates. However, only crude necrosis rates are reported and some papers do not report about radiation necrosis at all. We think there is insufficient information about the complication risk for routine use of schemes with a BED_{12} higher than 52 Gy (Table 2 and 3).
Whole brain irradiation added to SRT may improve local control rates [36]. As we were interested in local control rates after SRT alone, we omitted the studies that used SRT as a boost in all patients. In some of the 11 studies, however, WBI was added to SRT in selected patients for a variety of reasons, i.e., SRT for recurrence after WBI, SRT as a planned boost after WBI or WBI for recurrence after SRT. The indication for adding WBI to SRT was not always mentioned [34]. In nine of the eleven papers the percentage of the patients that had received WBI was only 0–15% (Table 1). Such a low percentage could not have had a major influence on local control rates. In the two studies that reported higher WBI rates, reported local control rates were low compared to the other studies. This also suggests minor influence of WBI on local control rates in these two studies, probably because in most of their patients SRT was not used as a boost after WBI. Based on this we think that our conclusions about local control effects of SRT doses are still valid, even if some of the patients from the 11 papers received additional WBI.
There is a debate whether the LQ formalism, and consequently the BED formula, can be used to predict the biological effect of the high fraction doses as applied in SRT for brain metastases [22,37]. Those opposing the use of the LQ formalism in this setting argue that tumor control probability after single fraction SRT in fact is much greater than expected based on the LQ model [37]. Brenner discussed that the LQ-model was well validated, experimentally and theoretically, for fraction doses upto 10 Gy, and would be reasonable for use upto about 18 Gy per fraction [22]. We observed that in the reviewed literature here single SRT doses upto 25 Gy were applied. Therefore, we applied the adjusted LQ model. In this limited amount of useful literature we found that with fraction doses in the range of 6–25 Gy, the BED_{12} has a relation with 12-month local control rates. We think that the LQC-BED concept is useful to develop treatment protocols for metastases, also for those larger than 3 cm that cannot receive high enough single-fraction doses because of expected toxicity.
Factors other than SRT dose can determine local control rates, such as tumor size, specification isodose, GTV–PTV margins and tumor type. In this literature study it was not possible to take into account the influence on local control of all these factors.
Local control has been reported to be influenced by tumor size [31,38–47]. However, this influence is difficult to quantify, because in many series lower doses are prescribed for larger metastases or prescribed doses vary widely. The effect of the tumor size was quantified in only one study, in which all brain metastases were treated with 20–24 Gy [25]. Twelve-month local control rates were 86% and 56% in metastases of less or more than 1 cm diameter, respectively. This implies that the distribution of tumors within each group of tumors receiving a uniform dose may influence the local control rate in that group.
In gamma knife series dose is often specified on the 50% isodose and in lineac series on the 80–100% isodose (Table 1). Local control may be influenced by the specification isodose. In the final report of RTOG 90-05 the authors state that patients treated on a linear accelerator were more likely to have local progression than those treated on a gamma knife [17]. The

observed difference in local control between the two machine types is probably related to the difference in dose specification. Looking at the results of this literature study we have to bear in mind the influence of dose specification, but we do not have data that enable us to correct for this factor.

A GTV–PTV margin of zero, as used in many SRT series, may lead to a lower dose in the GTV [48]. In one study a significant improvement of local control was reported after GTV–PTV margins were changed from 0 to 1 mm [49]. In the 11 papers we studied the margin was 0 mm in five out of seven single-fraction series and one out of four FSRT series. We cannot exclude that the generally higher local control rates in the FSRT series were not only due to the higher BED, but also due to the used margins, but the data are not sufficient to draw conclusions.

Finally, selection bias cannot be excluded as only 11 studies could be used all with a retrospective design. Presently we conduct a prospective study in our department with fixed doses according to tumor volume and three monthly follow-up including neurocognitive tests and perfusion MRI (personal communication).

Concluding, we found only 11 studies in the literature of the last 20 years that are helpful to study the dose–effect relationship in SRT for brain metastases. Twelve-month local control rates are excellent after single fraction SRT doses above 20 Gy, but disappointing after doses of 15 Gy or less. For brain metastases larger than 3 cm FSRT should be considered. The BED concept can be helpful to develop FSRT treatment protocols. For BED_{12} values of at least 40 Gy 12-month local-control rates of 70% and higher are found. A BED_{12} value of 40 Gy translates into a single fraction of 20 Gy, 2 fractions of 11.6 Gy or 3 fractions of 8.5 Gy.

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3c: LOCAL PROGRESSION AND PSEUDO PROGRESSION AFTER SINGLE FRACTION OR FRACTIONATED STEREOTACTIC RADIOTHERAPY FOR LARGE BRAIN METASTASES

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ABSTRACT

Purpose: The 1-year local control rates after single-fraction stereotactic radiotherapy (SRT) for brain metastases >3 cm diameter are less than 70%, but with fractionated SRT (FSRT) higher local control rates have been reported. The purpose of this study was to compare our treatment results with SRT and FSRT for large brain metastases.

Materials and methods: In two consecutive periods, 41 patients with 46 brain metastases received SRT with 1 fraction of 15 Gy, while 51 patients with 65 brain metastases received FSRT with 3 fractions of 8 Gy. We included patients with brain metastases with a planning target volume of >13 cm^3 or metastases in the brainstem.

Results: The minimum follow-up of patients still alive was 22 months. Comparing 1 fraction of 15 Gy with 3 fractions of 8 Gy, the 1-year rates of freedom from any local progression (54% and 61%, p=0.93) and pseudo progression (85% and 75%, p=0.25) were not significantly different. Overall survival rates were also not different.

Conclusion: The 1-year local progression and pseudo progression rates after 1 fraction of 15 Gy or 3 fractions of 8 Gy for large brain metastases and metastases in the brainstem are similar. For better local control rates, FSRT schemes with a higher biological equivalent dose may be necessary.

Stereotactic radiotherapy (SRT) is an established treatment modality for patients with brain metastases [1]. Local control of the metastases is the aim of treatment as progressive tumor growth may lead to new neurologic symptoms [2]. The dose that can be safely administered depends upon the size of the metastasis [3]. In Radiation Therapy Oncology Group (RTOG) study 90–05 the maximum tolerated single fraction dose for metastases with a diameter >3 cm was found to be 15Gy, as a higher dose of 18Gy was associated with an unacceptably high rate of grade 3–5 neurotoxicity. Progression after radiotherapy may be caused by proliferation of tumor cells but may also be a manifestation of radiation toxicity (pseudo progression). The distinction between these two types of progression is difficult to make on magnetic resonance imaging (MRI), but perfusion MRI may be helpful in this respect [4].
The 1-year local control of metastases >3 cm is reported to be 37–62% after 15 Gy [3, 5, 6]. With FSRT 1-year local control rates >70% were reported [7, 8]. However, a comparative study of SRT and FSRT for large brain metastases has not yet been published. Furthermore, only scarce data are available about the rates of pseudo progression after SRT or FSRT. We observed a disappointing 12-month local control rate of 37% after a single-fraction dose of 15 Gy in our patients with large brain metastases [6]. In an attempt to improve local control rates we embarked on an FSRT protocol in September 2007, treating this category of patients with 3 fractions of 8 Gy. The purpose of the present study is to compare the local control rates as well as the rates of pseudo progression between these two treatment protocols.

MATERIALS AND METHODS

PATIENTS

Two patient cohorts received SRT for brain metastases in two consecutive periods. In both cohorts we included patients with metastases with a planning target volume (PTV) of >13 cm^3 or metastases in or close to the brainstem. The prescribed dose was 15 Gy between June 2004 and January 2007 (group A) and 24 Gy in 3 fractions of 8 Gy (in 8 days) between September 2007 and September 2009 (group B).
To be able to study the effect of SRT dose on local control, we excluded the patients who had SRT as a boost after whole brain irradiation (WBI). Karnofsky performance scores (KPS) were determined prospectively and the RTOG recursive partitioning analysis (RPA) scores were determined retrospectively in all patients.

TREATMENT

Patients had a CT scan with 2-mm slice thickness while fixed in a relocatable stereotactic head frame (Brainlab AG Feldkirchen, Germany) [9, 10]. All patients also had an MRI planning scan (T1-weighted 3D MPRAGE after gadolinium administration; voxel size 1.1×1.1×1.3 mm^3). Co-registration of CT and MRI, contouring and treatment planning were done on Brainscan 5.31 or iPlan 4.0 (Brainlab AG Feldkirchen, Germany). The gross tumor volume (GTV) was defined as the volume of the contrast-enhancing tumor as visualized on the MRI scan. The PTV was created by 3D expansion of the GTV with 2 mm. All patients were treated on the Novalis, a dedicated linear accelerator (Brainlab AG Feldkirchen, Germany). Dynamic conformal arc was used as treatment technique for all metastases. Doses were prescribed to the 80% isodose. We allowed a maximum dose of 8 Gy (SRT) and 15 Gy (FSRT) to the optic system and a maximum dose of 15 Gy (SRT) and 24 Gy (FSRT) to the brainstem.

FOLLOW-UP

All patients were followed-up at 3-month intervals at the outpatient clinic as long as their condition allowed them to come. These follow-up visits were combined with MRI scans at 1.5 T (Siemens, Erlangen, Germany). The imaging protocol consisted of T1-weighted images

	Group A (1x15 Gy) n (%)	Group B (3x8 Gy) n (%)	Group A vs Group B
Patients (n)	41	51	
Sex Male Female	 15 (37%) 26 (63%)	 19 (37%) 32 (63%)	p=0.9
Age (year) <65 ≥65	 22 (54%) 19 (46%)	 29 (57%) 22 (43%)	p=0.8
KPS <90 ≥90	 21 (51%) 20 (49%)	 29 (57%) 22 (43%)	p=0.6
RPA class 1 2 3	 7 (17%) 30 (73%) 4 (10%)	 8 (16%) 43 (84%) 0	p=0.7
Primary tumor Lung Breast Melanoma Other	 19 (46%) 10 (24%) 2 (6%) 10 (24%)	 24 (47%) 8 (16%) 9 (18%) 10 (19%)	p=0.2
Number of brain metastases 1 >1	 20 (49%) 21 (51%)	 28 (55%) 23 (45%)	p=0.6
Treatment: No WBI SRT as salvage after WBI WBI as salvage after SRT	 29 (70%) 6 (15%) 6 (15%)	 32 (63%) 13 (25%) 6 (12%)	p=0.4

Table 1. Patient and treatment characteristics in both groups.
Group A received 1 fraction of 15 Gy.
Group B received 3 fractions of 8 GyKPS Karnofsky performance score, RPA recursive partitioning analysis, WBI whole brain irradiation, SRT stereotactic radiotherapy.

without and with gadolinium, T2 images and diffusion-weighted imaging. MR perfusion imaging, using a SE-EPI sequence, was performed when increase or recurrence of gadolinium enhancement was observed in lesions. Analysis of the MR perfusion data was performed by calculating the relative cerebral blood volume (r-CBV) maps and by comparing the r-CBV

maps with the post-gadolinium T1-weighted images. R-CBV maps were considered to be suggestive for viable tumor tissue when r-CBV in the enhancing part of the tumor was equal to or higher than cerebral gray matter (based on visual assessment by a neuroradiologist). Telephonic follow-up was done if patients were not able to visit the hospital anymore; however, information thus acquired was only used for survival analysis. Local control was calculated from the first day of (F)SRT. All MRI scans were reviewed and tumors were measured in three dimensions. Response to treatment was classified according to the Macdonald criteria [11]. The date of the first MRI showing any local progression was used as the date of progression. Pseudo progression was diagnosed when perfusion MRI showed no signs of viable tissue [4]. Tumor progression was defined as tumor proliferation not caused by pseudo progression, i.e., with MR perfusion imaging characteristics compatible with viable tissue. Tumor progression could be preceded by pseudoprogression. Endpoints were any local progression, tumor progression and pseudo progression.

	Group A (1x15 Gy) n (%)	Group B (3x8 Gy) n (%)	Group A vs Group B
Metastases (n)	46	65	
Primary tumor			
Lung	22 (48%)	26 (40%)	
Breast	11 (24%)	13 (20%)	
Melanoma	2 (4%)	10 (15%)	p=0.3
Other	11 (24%)	16 (25%)	
PTV Volume			
<13cm^3	11 (24%)	18 (28%)	
13-20 cm^3	17 (37%)	16 (25%)	p=0.4
>20cm^3	18 (39%)	31 (47%)	
Treatment			
No WBI	33 (72%)	42 (65%)	
SRT as salvage after WBI	7 (15%)	15 (23%)	p=0.6
WBI as salvage after SRT	6 (13%)	8 (12%)	

Table 2. Tumor characteristics in both groups.
Group A received 1 fraction of 15 Gy.
Group B received 3 fractions of 8 GyPTV planning target volume,
WBI whole brain irradiation, SRT stereotactic radiotherapy.

ANALYSES

Statistical analysis was performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). The Pearson X^2 test was used to analyze whether the characteristics of both cohorts were equally divided. Overall survival and local progression-free survival (LPFS) curves were calculated using the Kaplan–Meier method. For the calculation of the actuarial freedom from any progression only the first progression of a metastasis was used as an event. The logrank test was used for the univariate analyses.

RESULTS

PATIENTS, METASTASES AND TREATMENT

Group A consisted of 41 patients with 46 brain metastases and group B consisted of 51 patients with 65 brain metastases. The median follow-up of all patients was 5.3 months and the minimum follow-up of patients still alive was 22 months. Patient and treatment characteristics were equally divided between both groups (. Tab. 1). The tumor characteristics of both cohorts are shown in Tab. 2.

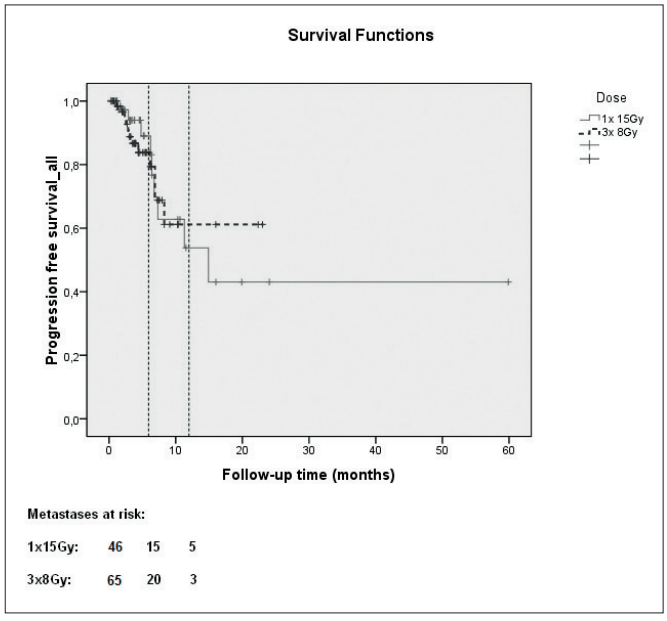

Figure 1. Theactuarial rate of freedom from all tumor progression in both groups of metastases. Tumor progression and peudo progression were considered as events. p=0.93

LOCAL PROGRESSION-FREE SURVIVAL (LPFS)

The actuarial rates of freedom from any local progression in group A and B are shown in Fig. 1. The 6- and 12-month local control rates were 89% and 54% with 1 fraction of 15 Gy and 84% and 61% with 3 fractions of 8 Gy. LPFS rates were not significantly different between the two groups (p=0.93). In two brain metastases tumor progression was preceded by pseudo progression. Only one resection of a progressive lesion was performed (in a patient from the SRT cohort). The histological diagnosis was radiation necrosis.

The actuarial freedom from tumor progression in groups A and B are shown in Fig. 2. Pseudo progression was not considered an event in this figure. The 6- and 12-month rates of freedom from tumor progression were 89% and 67% with 1 fraction of 15 Gy and 92% and 75% with 3 fractions of 8 Gy. There was no significant difference between both groups (p=0.27).

The actuarial rates of freedom from pseudo progression in group A and B are shown in Fig 3. The 6- and 12-month rates of freedom from pseudo progression were 93% and 85% with 1 fraction of 15 Gy and 91% and 75% with 3 fractions of 8 Gy. There was no significant difference between the two groups (p=0.25).

In a univariate analysis dose (15 or 24 Gy), KPS, PTV, previous WBI only and all WBI (previous or later) were correlated with the occurrence of all tumor progressions, pseudo progres

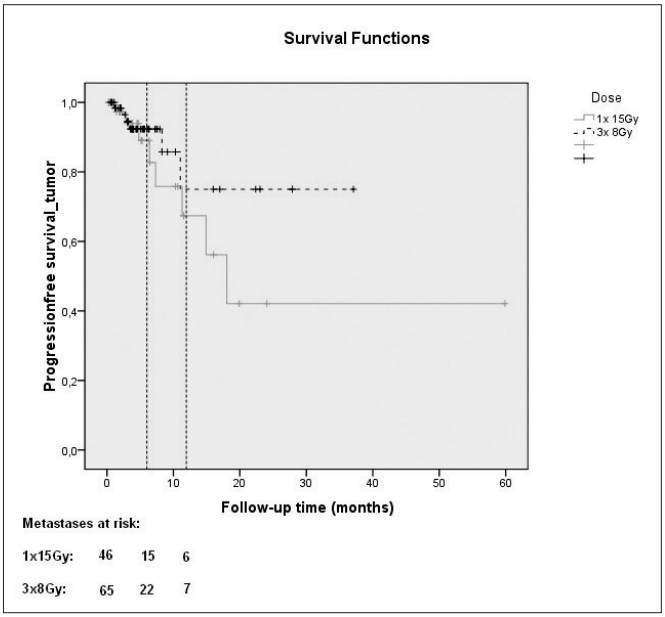

Figure 2. Theactuarial rate of freedom from tumor progression in both groups of metastases. Only tumor progressions, but not pseudo progressions were considered as events. p=0.27

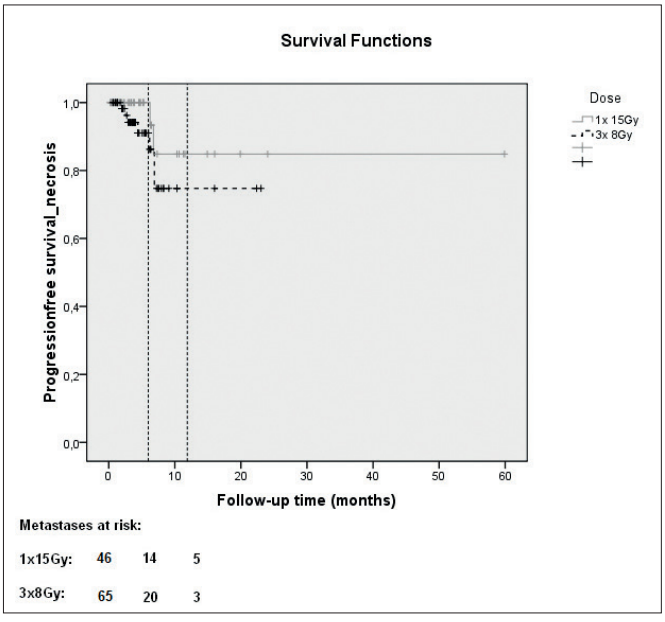

Figure 3. Theactuarial rate of freedom from pseudo progression in both groups of metastases. p=0.25

sion and tumor progression (Tab. 3). We found no relation between any type of progression and dose, KPS or tumor volume. However, after previous WBI a significantly higher rate of pseudo progression was found (p=0.02). Moreover, a higher rate of tumor progression was found with previous or later WBI. As this was the only significant relation, a multivariate analysis was not performed.

SURVIVAL

The median survival of all patients was 5.3 months. The 6- and 12-month overall survival rates were 41% and 23%, respectively. In the univariate analysis the only prognostic factor for survival was KPS (p=0.02). We found no difference in survival rates between group A and B (p=0.58).

DISCUSSION

This is a retrospective comparison of SRT (1 fraction of 15 Gy) and FSRT (3 fractions of 8 Gy) used in two consecutive cohorts of patients with large-sized brain metastases. Actuarial survival rates and rates of freedom from progression or pseudo progression were found not to differ significantly between 1 fraction of 15 Gy and 3 fractions of 8 Gy. Therefore, FSRT with 3 fractions of 8 Gy does not seem to be an improvement over 1 fraction of 15 Gy for large brain metastases and metastases in the brainstem.

Surgery may be the treatment of choice for large brain metastases, if feasible. SRT however is also an attractive option for patients with large metastases, although symptomatic improvement and local control are not optimal after single fraction treatment [6, 12, 13, 14]. There is no agreement on the optimal SRT dose for these tumors. Recently we performed a systematic literature search to summarize the evidence about the relation between SRT dose and local control [13]. We found that 12-month local control after SRT was highly dependent upon dose and was high after >21 Gy, but low after <15 Gy [13]. However, it is known from RTOG 90–05 that unacceptably high neurotoxicity rates are found after treating larger recurrent brain metastases (diameter >3 cm) with single doses >15 Gy [3]. Higher local control rates were reported after FSRT in larger metastases with acceptable rates of radiation toxicity (Tab. 4, [8, 15, 16, 17, 18]). Therefore, to improve the results of SRT of large brain metastases, FSRT is a logical step, enabling a higher tumor dose with a lower risk of neurotoxicity.

We decided to treat these patients with 3 fractions of 8 Gy, after we had observed the disappointing efficacy of 1 fraction 15 Gy. The rationale for this new scheme was the better biologically effective dose (BED) "profile" of the fractionated scheme [6]. The BED model describes the responses to ionizing radiation well at doses up to about 18 Gy [19, 20, 21]. The BED_2 values (for normal tissue, α/β = 2 Gy) for 1 fraction of 15 Gy and 3 fractions of 8 Gy are 127.5 Gy and 120 Gy respectively and the BED_{12} values (for tumor, α/β = 12 Gy) 33.8 Gy and 40 Gy respectively. Based on the BED model we initially expected an improved local control with less late toxicity. In hindsight these expected differences are probably too small to detect in the relatively small numbers studied here. To improve local control for brain metastases with a PTV >13 cm^3 it would be logical to use FSRT with a higher BED_{12}, keeping in mind that the rate of adverse treatment effects may also increase. In our department we decided to change the protocol for these large metastases to 3 fractions of 8.5 Gy, following the conclusions from our literature search [13].

As this is not a randomized comparison, conclusions from this study have to be viewed with caution. Local control was found to be independent upon PTV and all other factors that may influence local control are well balanced between the two cohorts. Therefore we think that it is justified to conclude that local control rates are similar with both dose schemes, with all well-known restrictions of a retrospective study.

		All local progressions	Tumor progression	Pseudo progression
Dose	1x15 vs 3x8 Gy	P=0.93	P=0.27	P=0.25
KPS	<90 vs ≥90	P=0.50	P=0.17	P=0.50
PTV Volume	<13cm^3 vs 13-20cm^3 vs >20cm^3	P=0.72	P=0.60	P=0.36
Previous and later WBI	Yes vs no	P=0.07	P=0.04[a]	P=0.02[b]
Only previous WBI	Yes vs no	P=0.02	P=0.63	P=0.02[c]

Table 3. Univariate analysis of prognostic factors for local progression.
Log rank: p value
[a] 6 out of 75 metastases without WBI developed tumor progression,
8 out of 36 metastases with WBI developed tumor progression.
[b] 3 out of 75 metastases without WBI developed pseudo progression,
6 out of 36 metastases with WBI developed pseudo progression.
[c] 6 out of 22 metastases with previous WBI developed pseudo progression,
3 out of 89 metastases without previous WBI developed pseudo progression.
No metastasis with WBI after SRT developed pseudo progression

Author	Diameter/volume	Dose (Gy)	BED_{12} (Gy)	12-month local control (%)	Radiation toxicity (%)
Vogelbaum [16]	3 - 4.5cm	1 x 15Gy	33.8	45	na
Ernst- Stecken [18]	1 - 5cm	5-6 x 7Gy	45-55.4	76	14% (V_{4Gy} <23cc)[c] 70% (V_{4Gy} >23cc)
Narayana [17]	2 - 5cm	5 x 6Gy	45	70	na
Higuchi [8]	3 - 4.5cm	3 x 10Gy	55	76	0[b]
Marchetti [15]	0.3 - 48.2cm^3	3 x 8Gy	40	59	2[b]
This series	76% > 3cm 76% > 3cm	1 x 15Gy 3 x 8Gy	33.8 40	54 61	15[a] 25[a]

Table 4. Results from the literature on SRT for large brain metastases
[a] pseudoprogression
[b] late radiation necrosis
[c] new or increasing necrotic lesions
na: not available
V4Gy: volume of tissue receiving at least 4Gy per fraction

An enlargement of the treated volume after radiotherapy may be caused by an increased proliferation rate of tumor cells but may also be a manifestation of radiation toxicity (pseudo progression). We prefer to use the term pseudo progression instead of radiation necrosis like it is used in gliomas, where real progression can also be preceded by pseudo progression [22]. The histology of this radiation effect usually is a chronic inflammatory reaction of brain tissue combined with necrosis of normal brain tissue and tumor tissue [23]. The distinction between real tumor progression and pseudo progression is difficult to make using standard morphologic MR imaging, but modern MR imaging techniques, especially perfusion MRI, may be helpful to differentiate viable tumor tissue from tissue with radiation effects [4, 24]. In our patients a substantial proportion of all progressions were diagnosed as pseudo progression. As the rate of pseudo progression was not significantly different between group A and B (15% versus 25% at 1 year), whereas the metastases in group B were slightly larger than those in group A, 3 fractions of 8 Gy is certainly feasible for the larger metastases.

Not much is known about ways to reduce the rate of pseudo progression. A relation has been reported between the rate of radiation necrosis and the V12 (volume of tissue that received a single dose of ≥12 Gy) [25, 26]. A lower BED to normal brain tissue and at the same time a higher BED to tumor tissue would be needed to reduce the rate of pseudo progression without compromising local control. To this end FSRT may be used, but more research is needed to find the optimal scheme.

An interesting finding in our study is the higher rate of pseudo progression in patients with prior WBI. This would imply that it would be safe to give higher biological doses than advised based on RTOG 90–05 if no prior WBI has been given. Until now, only a few and somewhat conflicting data are available on this issue. Chao *et al.* [5] retreated 111 patients with SRT for recurrence after WBI and found only two cases of radiation necrosis. Yang *et al.* [14] treated 70 patients with metastases >3 cm diameter with SRT, 33 of whom had previous WBI. After 2 months patients with previous WBI had slightly worse edema response and symptom relief than those without. Fourteen of 29 patients with imaging assessment >6 months after SRT had adverse radiation effects (48%), but the authors did not mention a relation with previous WBI.

We conclude that local control rates with 1 fraction of 15 Gy or 3 fractions of 8 Gy for large brain metastases are similar. Large brain metastases can be safely treated with a hypofractionated scheme, but the optimal dose remains to be determined.

Conflict of interest: No statement made.

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CHAPTER 4

Pseudo-progression and
tumor progression after SRT
of brain metastases

4a: PSEUDO-PROGRESSION AFTER STEREOTACTIC RADIOTHERAPY OF BRAIN METASTASES: LESION ANALYSIS USING MRI CINE-LOOPS

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ABSTRACT

Stereotactic radiotherapy (SRT) of brain metastasis can lead to lesion growth caused by radiation toxicity. The pathophysiology of this so-called pseudoprogression is poorly understood. The purpose of this study was to evaluate the use of MRI cine-loops for describing the consecutive events in this radiation induced lesion growth. Ten patients were selected from our department's database that had received SRT of brain metastases and had lesion growth caused by pseudo-progression as well as at least five follow-up MRI scans. Pre- and post SRT MRI scans were co-registered and cine-loops were made using post-gadolinium 3D T1 axial slices. The ten cine-loops were discussed in a joint meeting of the authors. The use of cine-loops was superior to evaluation of separate MRI scans for interpretation of events after SRT. There was a typical lesion evolution pattern in all patients with varying time course. Initially regression of the metastases was observed, followed by an enlarging area of new contrast enhancement in the surrounding brain tissue. Analysis of consecutive MRI's using cine-loops may improve understanding of pseudo-progression. It probably represents a radiation effect in brain tissue surrounding the irradiated metastasis and not enlargement of the metastasis itself.

Electronic supplementary material

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INTRODUCTION

Radiotherapy is an important treatment modality for almost all patients with primary or secondary brain tumors. Classically, response evaluation is done by measuring the size of the tumor on pre- and post treatment MRI and using the Macdonald criteria, the WHO criteria or RECIST criteria [1–3]. Following these criteria local progression is defined as an increase of at least 20–25 % in the size of the enhancing lesion. However, we now know that post treatment enlargement of the enhancing lesion cannot only be caused by tumor progression, but may also be due to so-called pseudo-progression. Pseudo-progression has been described first in high-grade gliomas, treated with chemoradiotherapy [4]. This observation has led to a proposal of updated response criteria for high-grade gliomas [5].
After stereotactic radiotherapy (SRT) of brain metastases a comparable phenomenon is encountered, also referred to as pseudo-progression by several authors [6, 7]. Consequently updated recommendations for response evaluation have been published for brain metastases as well [8]. However, it is unknown if the same pathogenesis underlies pseudo-progression in gliomas and brain metastases.
Pseudo-progression after SRT of brain metastases is considered to be a manifestation of late radiation toxicity, but what happens on the tissue level is largely unknown. Pseudo-progressive lesions have been reported to consist of radiation necrosis, but in general there is no consensus on the definition of and diagnostic criteria for radiation necrosis [9, 10]. Reported rates of radiation necrosis vary widely, due to the fact that there is no single definition [9–13]. In one report in ten patients who had undergone resection of pseudo-progressive lesions, the histological findings consisted of necrosis surrounded by an enlarging inflammatory infiltrate [14]. Still it is unclear if these lesions represent necrosis of tumor or surrounding brain tissue and therefore the nature of the growing lesion that we see on serial follow-up MRI scans is debated on. Especially for the technique of SRT it is important to know if pseudo-progression is caused by radiation toxicity of the brain.
This study deals with the underlying and unknown nature of the enlarging lesion in patients with pseudo-progression after SRT of brain metastases. To address this issue we used series of co-registered consecutive follow-up MRI scans of patients with pseudo-progression and combined these scans into cine-loops. We hypothesize that cine-loops are more helpful than static MRI scans in defining the location of treatment related changes, whether it is in the tumor or in the surrounding brain parenchyma.
The purpose of this study is to evaluate these cine-loops for getting more insight into the pathogenesis of pseudo-progression after SRT of brain metastases.

METHODS

TREATMENT AND FOLLOW-UP

Patients who presented with one to three brain metastases received SRT with Novalis (Brainlab AG, Feldkirchen, Germany) in our department if their Karnofsky performance score was at least 70. Our protocol and technique have been described elsewhere [7, 15]. The patients received either one fraction of 21 or 18 Gy or, alternatively, 24 Gy in three fractions of 8 Gy. In all cases the GTV was contoured on a T1 weighted contrast enhanced MRI, the CTV was equal to the GTV and a CTV-PTV margin of 2 mm was applied. Our policy was to perform follow-up MRI scans every three months after SRT if there were possible therapeutic implications, i.e. as long as the Karnofsky score of the patient was at least 70. In some patients an MRI scan was made already as early as one month after SRT.
The imaging protocol consisted of T1-weighted images without and with gadolinium, T2 images and diffusion weighted imaging (Siemens Magnetom, 1.5 Tesla). The contrast-enhancing tumor on the pre-SRT T1 MRI was considered the GTV and the post-SRT con-

trast enhancement in the treated area was called the "lesion" thereby expressing its uncertain nature. MR perfusion imaging, using a SE-EPI sequence, was performed in all cases. Analysis of the MR perfusion data was performed by calculating the relative Cerebral Blood Volume (r-CBV) maps and by comparing the color r-CBV maps with the post- gadolinium T1 weighted images. R-CBV maps were considered to be suggestive for viable tumor tissue when r-CBV in the enhancing part of the tumor was equal to or higher than that of cerebral gray matter (based on visual assessment of the color map by the neuroradiologist). Pseudo-progression was diagnosed radiologically when the perfusion MRI showed no signs of viable tissue [16]. Furthermore, in cases without histological proof, the above mentioned perfusion MRI characteristics had to be associated with self-limiting progression or regression of the lesion or in cases with ongoing progression at least one of the following radiological characteristics had to be present: (i) the lesion transgresses natural anatomic boundaries such as the cerebral falx, (ii) the lesion has a characteristic Swiss cheese pattern on post-contrast imaging, or (iii) the lesion has a necrotic center without contrast enhancement.

SELECTED PATIENTS

From our departmental SRT database (with data of all our cranial SRT patients from 2004) we selected 10 exemplary patients diagnosed with pseudo-progression. These were patients who had follow-up with at least five MRI scans during at least nine months after SRT for brain metastases and in whom we diagnosed pseudo-progression on either histological grounds or based on radiological findings highly suggestive for pseudo-progression as mentioned above.

MRI CINE-LOOPS

From the MRI series of these selected patients we used the post-gadolinium T1-weighted images. These post-treatment images were transferred to IPlan (Brainlab AG Feldkirchen, Germany), the planning system we use for SRT, and co-registered (fused) with the pre-treatment MRI. The metastatic lesion before SRT and the same lesion as it appeared on MRI after SRT were contoured on all consecutive MRI scans and the volume of these contoured lesions was determined in IPlan.

From each patient we selected the axial slice with the largest pre-SRT lesion diameter and selected the corresponding slices from this patient in the other available MRI scans. The series of consecutive images we collected in this way was used to make a cine-loop. To make a cine-loop we copied the selected anonymized MRI slices to Microsoft Windows Movie Maker (Microsoft Corp. Redmond USA), put them in chronological order and used the fading mode for the transitions between the separate slices. The examination dates were added to the separate MRI slices on the loops. These dates, but not the length of the cine-loops, marked the duration of the events.

INTERPRETATION OF THE CINE-LOOPS

A team of three radiation oncologists, a technician and a neuroradiologist interpreted all ten cine-loops in conference. Before examining the cine-loops they had confirmed the diagnosis pseudo-progression in all cases. In each cine-loop the team determined if it was possible to discern the metastasis from radiation induced normal tissue effects and determined at what moment this lesion was regressing, stable or progressing. Finally, the sequence of events was described from each movie and correlated with the measured volume changes.

RESULTS

CHARACTERISTICS OF PATIENTS AND GROWING LESIONS

Table 1 shows the characteristics of the studied patients. In all ten cases the perfusion MRI

was compatible with pseudo-progression, in five cases (pts nr 1,3,4,5 and 8) the lesion growth was self-limiting in the observation period and in one case the growing lesion transgressed the falx (pt nr 9). Histological examination of the enhancing tissue had been performed in two patients (pts nr 3 and 8) and confirmed the existence of necrotic tissue without residual tumor cells. Figure 1 shows the development of the lesion volume over time following treatment.

Patient	Gender	Age	Primary Diagnosis	Metastasis Volume (cm3)	SRT Dose	WBI	Steroids	Diagnosis of pseudo-progression	Symptoms	Interval (months)	Last FU
1	male	58	esophagus	0.8	1x21Gy	no	no	p, r	no	6	AWD
2	female	57	lung	1.0	1x21Gy	no	no	p	paresis	14	DOD
3	female	58	ovarian	2.3	1x21Gy	no	no	p, h, r	seizures	30	AWD
4	female	57	breast	2.8	1x21Gy	yes	no	p, r	seizures	14	DOD
5	male	74	lung	3.4	1x21Gy	no	yes	p, r	no	6	AWD
6	male	52	renal	5.4	1x18Gy	no	yes	p	paresis	22	DOD
7	female	57	lung	6.0	1x18Gy	no	no	p	paresis	39	DOD
8	male	66	renal	6.8	3x8Gy	no	yes	p, h, r	seizures, headache	1	DOD
9	female	69	breast	11.4	3x8Gy	no	yes	p, f	cognitive	7	DOD
10	female	57	breast	13.8	3x8Gy	yes	yes	p	ataxia	5	AWD

Table 1. Patient and treatment characteristics
WBI: **Whole Brain Irradiation,** ***Steroids:*** **use of steroids during the lesion growth,** ***Diagnosis of pseudo-progression:*** **information supporting pseudo-progression as explanation for lesion growth,** ***P:*** **perfusion MRI (including standard diagnostic MRI),** ***h:*** **histology (necrosis),** ***f:*** **lesion crossing the falx,** ***r:*** **regression after the lesion growth,** ***Symptoms:*** **symptoms caused by the growing lesion,** ***Interval:*** **time interval between SRT and first MRI with lesion growth in months,** ***Last FU:*** **status of the patient at last follow-up,** ***AWD:*** **alive with disease,** ***DOD:*** **dead of disease**

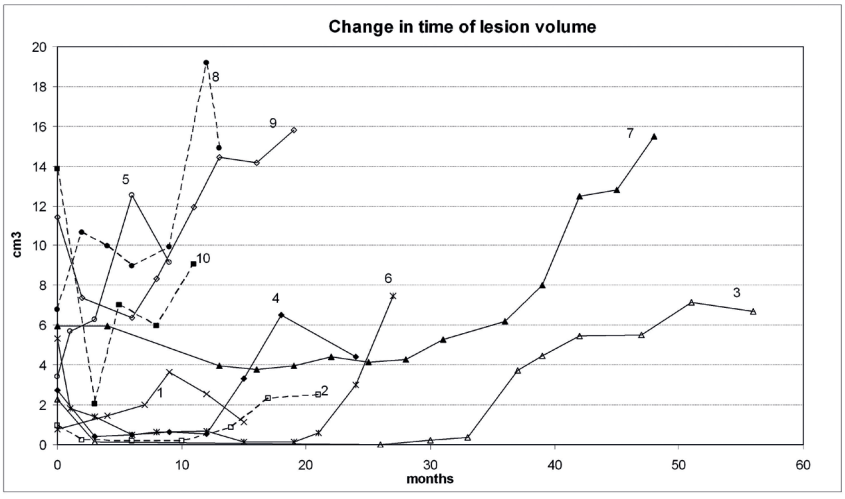

Figure 1. The development of the lesion volume in time after treatment. Each line has a number that corresponds to the patient number in Table 1.

CINE-LOOPS VERSUS SEPARATE MRI SCANS

The team agreed that there was additive value of the cine-loops over separate MRI scans, with or without image fusion, in giving more insight into the sequence of events over time.
Figure 2 illustrates that it is difficult to understand the evolution of the lesion in separate MRI scans without image fusion. This figure shows a series of axial slices from non co-registered MRI scans of patient 5. In the lower row the corresponding color maps from the perfusion MRI show a low rCBV in the area of the lesion growth, indicating pseudo-progression.
Figure 3 illustrates that even using co-registered MRI scans it is difficult to separate between changes in the metastatic lesion and in the normal brain tissue. This figure shows a series of axial slices from co-registered MRI scans of patient 7.
Online resources 1 and 2 are the cine-loops of patient 5 and 7, respectively. They illustrate that the development over time of the growing lesion can be recognized better by watching the MRI scans in the form of a loop. The metastasis can be seen to regress and the lesion growth that follows can be recognized as growing enhancement in brain tissue and not in the metastasis itself.

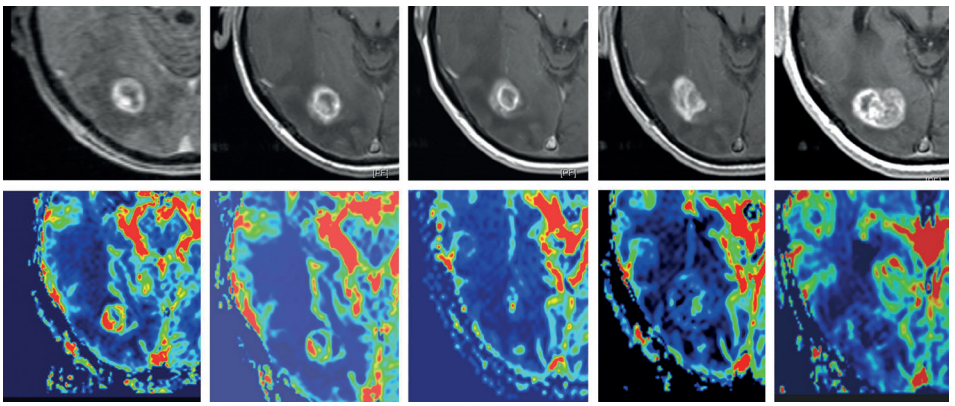

Figure 2. Five consecutive non co-registered MRI scans of patient 5. In the upper row the non co-registered MRI scans and in the lower row the color maps of the corresponding slices of the perfusion MRI scans, from left to right before SRT and 1, 3, 6 and 8 months after SRT.

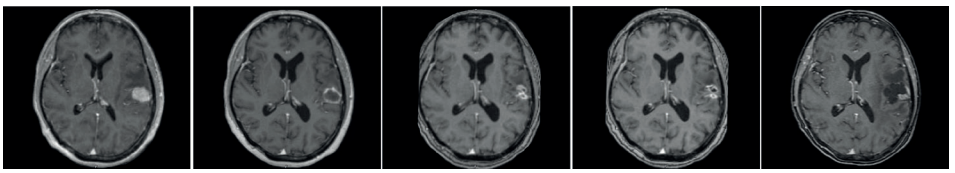

Figure 3. Five consecutive co-registered MRI scans of patient 7, from left to right before SRT, after 3 months, 1, 2 and 4 years. Development of a cystic lesion, compatible with late radiation necrosis of brain tissue. Especially in the first two years it is difficult to separate changes in tumor and brain tissue based on static images.

INTERPRETATION OF THE CINE-LOOPS

In Table 2 the interpretations by the team of the ten cine-loops are summarized. A similar pattern was recognized in all ten cases. The team agreed that in all cases the lesion growth was caused by progressive enhancement of the brain tissue surrounding the metastasis at the time of SRT. In all cases this lesion growth was preceded by regression of the metastasis. In five cases enhancement of surrounding brain tissue started when the visible regression of the metastasis was only partial and complete regression could not be ascertained. In the other five

cases the brain tissue enhancement started later, after complete regression of the metastasis had become visible. Furthermore, the development of a considerable edema reaction was noticed around the growing lesions in nine patients.

	Regression phase	Progression phase
Patient 1	CR of the metastasis	Growing of rim enhancement of brain surrounding necrotic center followed by regression of the rim enhancement
Patient 2	CR of the metastasis	Growing rim enhancement of brain surrounding necrotic center.
Patient 3	CR of the metastasis	Growing enhancement of brain tissue.
Patient 4	CR of the metastasis	Growing rim enhancement of brain surrounding necrotic center.
Patient 5	PR of the metastasis and beginning enhancement of brain tissue	Growth of enhancement of brain tissue and further regression of the metastasis, finally regression of enhancement of brain tissue
Patient 6	CR of the metastasis	Growth of enhancement of brain tissue.
Patient 7	PR of the metastasis, later stable enhancement of (probably) brain tissue for 15 months	Growth of enhancement of brain tissue, later cyst formation , compatible with necrosis.
Patient 8	Growth of metastasis in 1st month, later PR of the metastasis	Growth of enhancement of brain tissue followed by regression of enhancement of brain tissue.
Patient 9	PR of the metastasis	Formation of necrotic tumor, later filled in with enhancing tissue, still later growth of enhancement of brain tissue (enhancement crossing the falx).
Patient 10	PR of the metastasis	Growth of enhancement of brain tissue and formation of necrosis.

Table 2. Interpretation of the cine-loops.
CR complete regression, PR partial regression.

DISCUSSION

In this study we used MRI cine-loop analysis to evaluate radiation induced lesion growth after SRT for brain metastases. Although the interpretation of the cine-loops is a subjective assessment of the changes in time of the images, to our opinion this interpretation is not essentially different from the assessment of the images of a single MRI scan. We found that MRI cine-loops were superior to sequential MRI scans in understanding the sequence of events after SRT. By this method it was possible to make the distinction between effects on the tumor itself (regression) and on the surrounding brain tissue (new enhancement developing after a varying time interval). We argue that most probably this type of lesion growth is not an effect on the metastasis itself, but a radiation effect on the surrounding normal brain tissue, preceded by regression of the metastasis. Although the time intervals between SRT and start of lesion growth varied widely, the events in all patients were strikingly similar.

We are not aware of comparable reports of the use of MRI cine-loops in the follow-up of irradiated brain metastases, but the use of movies composed of serial images to study changes in time is well established. Representation of tumor or organ motion by 4D CT or 4D MRI is common practice [17, 18]. Time-lapse imaging has also been used to visualize disease progression micro-endoscopically [19].

The diagnosis of pseudo-progression was based on diagnostic MRI with additional perfusion MRI in all our patients, whereas other imaging features to support this diagnosis was available in six of the patients (Table 1) [16]. These features were regression of the lesion after the growth phase in five patients and lesion growth crossing the falx (following the pattern of the isodose lines of the treatment plan) in one patient. In the remaining four patients there was development into a typical necrotic lesion. Although histology is the golden standard for the diagnosis, the follow-up of these patients with imaging was further proof that there was no recurrent growth of metastasis.

In 15–32 % of the metastases a growing lesion may be seen on follow-up MRI at a certain point in time after SRT [7, 10, 14]. The cause of this volume increase is often a treatment effect (pseudo-progression), but what actually happens at the histopathology level has not been completely clarified. Pseudo-progression may be regarded as a manifestation of tumor necrosis. This view is supported by a recent publication, in which metastases from radiosensitive primary tumors (lung, breast, colon, other) were more likely to increase in size during the first 12–18 months post-SRT than metastases from radioresistant tumors (melanoma, renal) [14]. If the nature of the primary tumor determines the likelihood of post-SRT swelling, then the swelling could very well be derived from tumor tissue. However, against this view stands the finding that necrosis rates increase with increasing V12 (volume of tissue that received 12 Gy), indicating that more irradiated normal tissue leads to more necrosis and that the growing lesion would probably be derived from normal brain tissue [9]. A further argument supporting this last view is the observation, as we also did in this study, that the necrotic lesion growth is preceded by a complete disappearance of the metastasis. This makes it very unlikely that the growing lesion is still derived from tumor tissue. Therefore, evaluating serial MRI scans using MRI cine-loops of these relatively long-term brain metastasis survivors was not only helpful in understanding the sequence of events, but also in unraveling the pathogenesis. Our interpretation of the cine-loops was that the growing enhancement developed in brain tissue surrounding the metastasis before SRT and, upon regression of the metastasis, spread into the area where the metastasis was found previously.

Radiation effects to the normal brain have classically been divided into three phases. Acute reactions are mainly edema and occur weeks after the start of radiotherapy, early-delayed reactions are edema and/or demyelination and appear within weeks to some months after radiotherapy and late delayed reactions occur three months to many years after treatment [20]. The most important late-delayed radiation effect is necrosis and this can be reversible,

irreversible or progressive [20, 21]. In our patients lesion growth started after three until 36 months after SRT and should therefore be classified as a late radiation effect. Although necrosis was proven with histology in only two of our 10 patients, necrosis was also likely in the eight non-resected cases. Patel *et al.* described the results of histologic examination of 10 pseudo-progressive lesions that had been resected at salvage surgery [14]. In all cases there was a center of coagulative necrosis surrounded by an area of vascular hyalinization that corresponded with the rim of contrast enhancement. In the adjacent brain tissue reactive gliosis and demyelination was observed. Reactive astrocytes in this perinecrotic area have been found to produce Vascular Endothelial Growth Factor (VEGF) [22]. This VEGF is thought to be the cause of the perilesional edema and the vascular proliferation that is visible in the cine-loops as the growing enhancing lesions.

As MRI cine-loops can only be made after a number of follow-up scans have been made, they can in our view not be used for clinical decision making when lesion growth is starting to be visible after SRT. However, we think it is relevant to know if pseudo-progression is radiation toxicity of the brain or an effect on the tumor itself. If it is an effect on the tumor itself we would have to accept it, but if it is a radiation effect on surrounding normal brain, a reduction of the volume of irradiated brain might be indicated, for example by reducing margins and trying to achieve the steepest dose fall-off.

Clinically there are similarities with pseudo progression in glioma patients after radio-chemotherapy as this lesion growth is also considered a radiation effect [4]. However, differences between post-radiation lesion growth in gliomas and brain metastases are that local recurrences are much more common in gliomas and that gliomas usually do not show tumor regression before lesion growth. Moreover, radiotherapy is delivered with different biologically effective doses to the brain. Therefore, we assume that pseudo progression in gliomas is to some extent a different phenomenon. Evaluation of serial MRI scans using cine-loops might be helpful to understand pseudo progression in gliomas as well.

CONCLUSION

We found that evaluation of serial MRI scans using MRI cine-loops provided better understanding of pseudo-progression that develops after SRT of brain metastases. We argue that this radiation induced lesion growth is probably not an effect on the metastasis itself, but a radiation effect on the surrounding normal brain tissue.

Conflict of interest: R. Wiggenraad has received speakers fee from Brainlab.

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4b: LESION GROWTH AFTER SRT OF BRAIN METASTASES A CLINICAL FOLLOW-UP STUDY

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submitted

ABSTRACT

Background: Stereotactic radiotherapy (SRT) of brain metastases results in regression of most treated metastases, but subsequent lesion growth may occur and is caused by tumor progression or pseudo-progression. The purpose of this study is to assess the clinical course of brain metastasis patients developing lesion growth after SRT.

Methods: The clinical course of all patients who received SRT for brain metastases from 2009 through 2012 and who had post-SRT lesion growth was retrospectively studied. All follow-up MRI scans were reviewed and the nature of lesion growth was classified as pseudo-progression, tumor progression or progression of uncertain cause (puc).

Results: SRT was applied in 237 patients with 407 brain metastases. The median follow-up period was 40.7 months.
Of the 65/237 patients (27%) with post-SRT lesion growth 57% (37/65), 14% (9/65) and 29% (19/65) had pseudo-progression, tumor progression and puc, respectively.
Neurological symptoms occurred at lesion growth in 70% (26/37), 100% (9/9) and 95% (18/19) of patients with pseudo-progression, tumor progression and puc. After the first lesion growth more patients with tumor progression improved clinically ($p<0.01$), because more underwent surgery, more patients with pseudo-progression remained asymptomatic ($p=0.04$), but the number of patients that remained symptomatic was similar between the groups ($p=0.47$).
Median survival after lesion growth of patients with pseudo-progression and tumor progression was also similar (8.6 versus 13.3 months, $p=0.7$).

Conclusion: Patients with symptomatic pseudo-progression or local tumor progression after SRT have a similar clinical course. However, patients with asymptomatic pseudo-progression have a more favorable clinical course and may remain asymptomatic.

INTRODUCTION

Stereotactic radiotherapy (SRT) of brain metastases results in regression or stabilization of the majority of treated metastases. However, up to one third of the irradiated metastases is reported to show an increase in volume on follow-up MRI scan 1. This post treatment lesion enlargement can be caused by tumor progression, but may also be due to so-called pseudo-progression.

Pseudo-progression is thought to be a manifestation of radiation necrosis of the brain surrounded by an enlarging inflammatory infiltrate [1, 2]. It is difficult to differentiate tumor progression from pseudo-progression with a conventional diagnostic follow-up MRI scan. Advanced imaging modalities such as perfusion MRI, PET and SPECT may be helpful to make the distinction [3]. However, there is still no consensus about imaging criteria for pseudo-progression after SRT. This lack of consensus and also the wide range in used SRT doses and techniques may explain why reported rates of pseudo-progression or radiation necrosis after SRT vary from less than 5% to more than 50% [4-6]. With the current diagnostic methods it is difficult to determine the cause of a growing lesion after SRT, but its presence has a profound impact on the clinical management of these patients. Anti-tumor treatment should be considered if tumor progression is presumed. On the other hand, if the cause of the enlargement is uncertain and pseudo-progression is suspected, no further anti-tumor treatment is indicated. In these cases it is uncertain whether the lesion will continue to grow and if treatment is necessary.

So far, the clinical course after post-SRT lesion growth has not frequently been described in detail [7, 8]. In a small randomized study on the effect of bevacizumab for radiation necrosis none of the seven placebo-treated patients showed an improvement of neurologic symptoms, whereas all patients treated with bevacizumab did [9]. Spontaneous regression has been reported in up to 39% of radionecrotic lesions after fractionated radiotherapy, but it is not exactly known how many of these patients improved clinically [10]. The purpose of this study was to improve insight into the clinical course of patients with a growing lesion after SRT of brain metastases and to compare the clinical course of patients with tumor progression and with pseudo-progression.

METHOD

PATIENTS AND TREATMENT

In this retrospective study we included all consecutive patients with brain metastases who were treated in the Radiotherapy Centre West with SRT in the years 2009 through 2012. Clinical data were collected retrospectively by the patients' physicians and anonymized for further processing. Therefore, according to Dutch law, ethics committee consent was not needed. Patients were selected for this follow-up study if an MRI, made before December 1st 2013, revealed enlargement of at least one of the treated metastases compared to the previous MRI. All enlarging lesions were included, even the enlarging lesions that initially regressed and subsequently did not catch up to the baseline volume before SRT.

Patients who presented with one to three brain metastases and had a Karnofsky Performance Score (KPS) of at least 70 received SRT with the Novalis linear accelerator (Brainlab AG, Feldkirchen, Germany). The patients received either one fraction of 21Gy, 18Gy, or 15 Gy, or three fractions of 8Gy or 8.5 Gy. The planning target volume (PTV) and the location of the metastasis determined the dose we prescribed. Dose prescription was on the 80% isodose line. In all cases no margin was applied between the gross tumor volume (GTV) and the clinical target volume (CTV) and a margin of 2mm between CTV and PTV.

CLINICAL FOLLOW-UP

The patients were seen at our outpatient clinic every three months as long as their condition allowed them to come. Clinical follow-up data of the patients with growing lesions after SRT were retracted from the medical records. Further information from other treating physicians was obtained by telephone. Patients alive were followed until December 1st 2014. Symptoms attributed to lesion growth were classified as neurological deficits, seizures or headache, with the most severe one used for clinical follow-up. The evolution of symptoms after the establishment of the lesion growth was classified as follows: improved, stable without symptoms, stable or worsening with symptoms, or unknown. The cause of death was determined on clinical grounds.

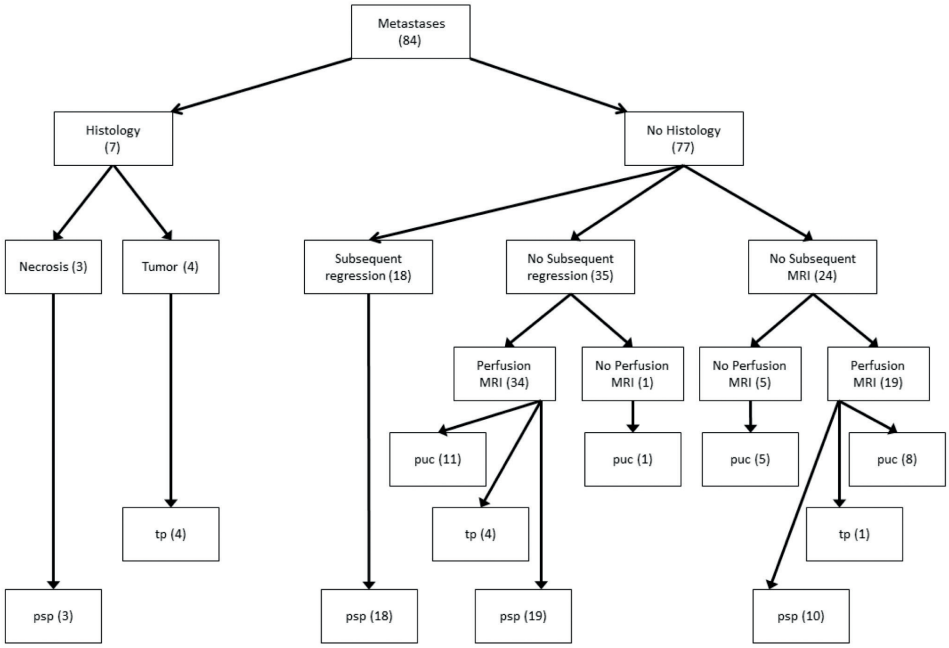

Figure 1. Diagnostic tree of the 84 progressive lesions. No histological diagnosis was available of 77 lesions. In 18 of these lesions subsequent regression was determined, indicating pseudo-progression. In 24 lesions no subsequent MRI was available after the first MRI with progression, but a perfusion MRI was available in 19 lesions, 10 of which were diagnosed as pseudo-progression. In 35 lesions further follow-up MRI-scans were available, in 19 lesions pseudo-progression was diagnosed based on follow-up perfusion studies. In six lesions the diagnosis was uncertain because there was no histology, no spontaneous regression and no perfusion MRI.
psp: pseudo-progression, tp: tumor progression, puc; progression of uncertain cause.

IMAGING FOLLOW-UP

We performed MRI scans every three months after SRT if there were possible therapeutic implications, i.e. as long as the KPS of the patient was at least 70. The maximum interval between SRT and the first MRI scan was three months, but an earlier MRI was allowed.
Standard imaging protocol consisted of T1-weighted images without and with gadolinium, T2-weighted images and diffusion-weighted imaging (Siemens Magnetom, 1.5 Tesla). MR perfusion imaging, using a GE-EPI (Echo Planar Imaging) sequence, was additionally performed in most follow-up visits in our hospital. The contrast enhanced T1 series from all follow-up MRI scans of the patients with these selected lesions were introduced into iPlan

4.5 (Brainlab AG, Feldkirchen, Germany). The contrast-enhancing tumor on the pre-SRT T1 MRI was considered the GTV and the post-SRT contrast enhancement in the treated area was called "lesion" (to express its uncertain nature). The selected contrast enhancing lesions were contoured on all axial slices by a radiation-oncologist (RW). This resulted in a 3D lesion volume on all follow-up MRI scans.
Analysis of MR perfusion data was performed by calculating the relative Cerebral Blood Volume (r-CBV) maps and by comparing the color r-CBV maps with the post-gadolinium T1-weighted images. R-CBV maps were considered to be suggestive for viable tumor tissue when r-CBV in the enhancing part of the tumor was equal to or higher than that of cerebral gray matter (based on visual assessment of the color map by a neuroradiologist). Pseudo-progression was diagnosed radiologically in growing lesions when the perfusion MRI showed no signs of viable tissue [11-13]. Additional MRI characteristics, such as a rim of contrast enhancement with a necrotic center or a characteristic Swiss cheese pattern were only considered supportive for the diagnosis pseudo-progression. Cases with significant MR artifacts due to hemosiderin in the lesion were categorized as progression of uncertain cause (puc).
All available MRI series including the perfusion data were reviewed independently by two experienced neuro-radiologists (GL, CM). Discordant results between the two reviewers were resolved by consensus (options were tumor progression, pseudo-progression or puc).

DIAGNOSTIC CRITERIA FOR PSEUDO-PROGRESSION OR TUMOR PROGRESSION AS THE CAUSE OF LESION GROWTH

To determine the clinical course of patients with growing lesions after SRT, we used all available diagnostic information regarding the irradiated metastases, including the information that became available after the date of lesion growth. Pseudo-progression or tumor progression was diagnosed based on histological examination if resection of the growing lesion was performed. Without histological confirmation pseudo-progression was diagnosed if the growing lesion subsequently showed regression or remained stable for more than three months. In cases without histological confirmation and without subsequent regression or stabilization the diagnosis was based on perfusion MRI. For this, both neuro-radiologists had to agree that the perfusion MRI data were indicative for a specific diagnosis. In the remaining cases we concluded that the cause of progression was uncertain (puc).

STATISTICS

Differences between categorical variables were determined using the Fisher exact test or the Chi-square test. An independent samples T-test was used for the continuous variable CTV.
Overall survival curves for the different diagnostic groups (pseudo-progression, tumor progression, puc) were calculated using the Kaplan-Meier method. Differences were analyzed using the log-rank test. The date of the first MRI showing lesion growth was considered the date of progression.
Overall survival time was calculated from the first day of SRT.
Time between pseudo-progression and regression and survival time after progression were calculated from the date of the first MRI showing pseudo-progression and progression respectively. For all analyses, we used SPSS Statistics version 20.0 (IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp.). P-values ≤ 0.05 (two-sided) were considered statistically significant for all tests.

RESULTS

From 2009 through 2012 SRT was performed in 237 patients; 407 brain metastases were treated (range 1-5 metastases per patient). The median follow-up of all patients still alive was 40.7 months (Interquartile Range (IQR) 26.6-44.8 months).

	All metastases without progression, no. (%)	All progressive metastases, no. (%)	p-value
Total	323	84	
Primary tumor			0.4
Breast	36 (11%)	15 (18%)	
Lung	164 (51%)	40 (47%)	
Colorectal	22 (7%)	8 (10%)	
Renal	29 (9%)	7 (8%)	
Melanoma	30 (9%)	8 (10%)	
Others	42 (13%)	6 (7%)	
Mean (SD) GTV volume	5.64 (8.09) cm^3	7.57 (7.87) cm^3	0.05
Dose			<0.01
21 Gy	184 (57%)	32 (38%)	
≤18 Gy	57 (18%)	18 (21%)	
3x8 /3x8.5 Gy	82 (25%)	34 (41%)	

Table 1a. Characteristics of the metastases and the SRT doses.

	Patients without progressive lesions, no. (%)	Patients with progressive lesions, no. (%)	p-value
Total	172	65	
Gender			0.4
Female	91 (53%)	39 (60%)	
Male	81 (47%)	26 (40%)	
Primary tumor			0.9
Breast	20 (12%)	10 (15%)	
Lung	83 (48%)	32 (49%)	
Colorectal	15 (9%)	5 (8%)	
Renal	16 (9%)	5 (8%)	
Melanoma	15 (9%)	7 (11%)	
Others	23 (13%)	6 (9%)	
Performance (KPS)			<0.01
≥90	71 (41%)	41 (63%)	
<90	101 (59%)	24(37%)	

Table 1b. Patients' characteristics.

I: ESTABLISHMENT OF LESION GROWTH

METASTASES

Lesion growth after SRT was found in 84 of the 407 (21%) brain metastases. Table1a shows the characteristics of the treated metastases and the given SRT doses. There was no difference with respect to the distribution of primary tumor types between growing and non-growing metastases. The metastases that later became progressive had a significantly larger initial volume (7.57 cm^3 versus 5.64cm^3, p=0.05) and consequently had received different SRT doses.
Figure 1 schematically shows the pathways taken to reach a diagnosis in the 84 progressive metastases. Progressive lesions were classified as pseudo-progression, tumor progression and puc in 59% (50/84), 11% (9/84) and 30% (25/84) of the cases.
Pseudo-progression was diagnosed in none of the melanoma metastases. There were no further differences between the lesions diagnosed as pseudo-progression, tumor progression and puc; GTV and SRT dosage were similar.
The plots in figure 2a show the time to local progression from the date of SRT, separately for the diagnostic groups.

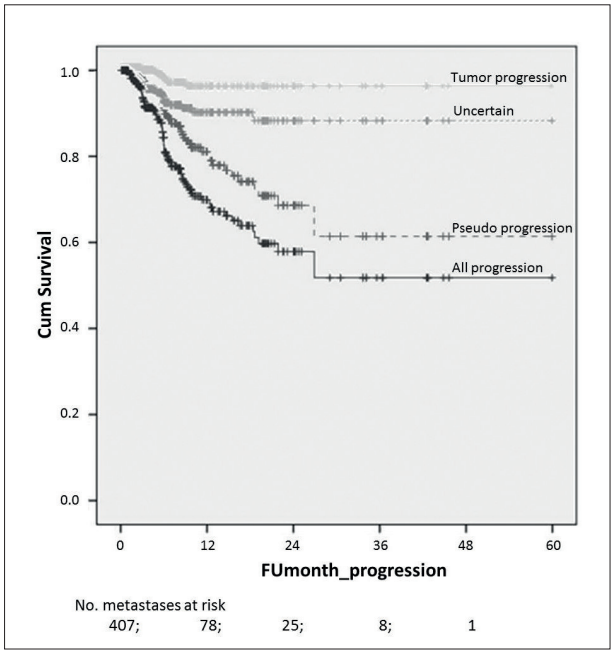

Figure 2a. Time to any local progression, pseudo-progression, tumor progression and progression of uncertain cause (puc) after SRT of all treated metastases.

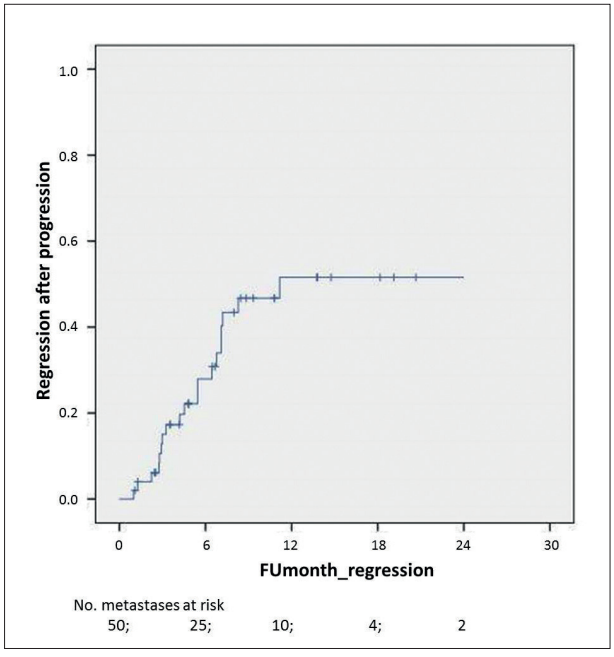

Figure 2b. Time to regression after pseudo-progression in the 50 pseudo-progressive metastases.

Actuarial progression rates after SRT of all treated metastases at 6 and 12 months were 17% and 30% for all progressive lesions, 9% and 19% for pseudo-progressive lesions, 2% and 4% for tumor progression and 7% and 10% for puc, respectively.
Spontaneous regression of the lesion after the growth phase was seen in 40% (20/50) of the lesions with pseudo-progression after a median period of 11.2 (IQR 5.5 – 28.2) months. Figure 2b shows the time to regression after pseudo-progression in the 50 pseudo-progressive metastases. The actuarial 6- and 12-month regression after progression rates were 28% and 52%, respectively.

PATIENTS

Lesion growth after SRT was found in 27% of the patients (65/237). Table 1b shows the patients' characteristics. Patient groups with or without a progressive lesion were comparable with respect to gender and types of primary tumors, but the initial performance status was significantly better in the patient group with a progressive lesion (63% of the patients with a progressive lesion had a KPS≥90 versus 41% of the patients without; p<0.01).
Pseudo-progression, tumor progression and puc was diagnosed in 57% (37/65), 14% (9/65) and 32% (21/65) of the patients with lesion growth. Two patients had both a pseudo-progressive lesion and a puc lesion.
Table 2a shows the main clinical symptoms that were attributed to the progressive lesions. The distribution of symptoms was not significantly different between the three diagnostic groups (p=0.26).

Main symptom/sign	Patients with pseudo-progression (n=37)	Patients with tumor progression (n=9)	Patients with progression of uncertain cause (n=19)	All patients (n=65)
Neurologic deficit	19 (51%)	7 (78%)	12 (63%)	38 (59%)
Headache	3 (8%)	2 (22%)	4 (21%)	9 (14%)
Seizures	4 (11%)	0	2 (11%)	6 (9%)
No symptoms/signs	10 (27%)	0	1 (5%)	11 (17%)
Unknown	1 (3%)	0	0	1 (2%)

Table 2a. Main symptoms attributed to the lesion growth.

Clinical course	Patients with pseudo-progression (n=37)	Patients with tumor progression (n=9)	Patients with progression of uncertain cause (n=19)	All patients (n=65)
Improvement	3 (8%)	4 (44%)	1 (5%)	8 (12%)
Stable, no symptoms	13 (35%)	0	1 (5%)	14 (22%)
Symptoms, stable or worse	19 (51%)	5 (56%)	13 (68%)	37 (57%)
Unknown	2 (5%)	0	4 (21%)	6 (9%)

Table 2b. Clinical course of patients after initial lesion growth.

Cause of death	Patients with pseudo-progression (n=37)	Patients with tumor progression (n=9)	Patients with progression of uncertain cause (n=19)	All patients (n=65)
Number of deaths	30/37 (81%)	8/9 (89%)	19/19 (100%)	57/65 (88%)
Systemic disease	17 (57%)	3 (38%)	8 (42%)	28 (49%)
Local tumor progression	0	3 (38%)	1 (5%)	4 (7%)
Distant brain progression	4 (13%)	2 (25%)	1 (5%)	7 (12%)
Related to pseudo-progression	4 (13%)	0	0	4 (7%)
Bleeding in the lesion	1 (4%)	0	2 (11%)	3 (5%)
Unknown	4 (13%)	0	7 (37%)	11 (19%)

Table 2c: Cause of death in patients with lesion growth.

II: CLINICAL COURSE AFTER LESION GROWTH

Table 2b shows data on the clinical course after initial lesion growth.
The clinical course of the three groups of patients was significantly different (p=0.002). Improvement of the main symptoms was seen more often in patients with tumor progression (44%) than in patients with pseudo-progression (8%) or those with puc (5%) (p<0.01). A possible explanation of this difference is that more patients with tumor progression had surgery of the growing lesion (44%) than patients with pseudo-progression (8%) or puc (0%) (supplementary table). Of the 8/65 patients that showed symptomatic improvement, 4 patients had surgery, 3 patients received corticosteroids and in one patient complete recovery occurred spontaneously after lesion regression 14 months after initial lesion growth.
Significantly more patients with pseudo-progression remained clinically stable without symptoms (13/37, 35%) than patients with tumor progression (0/9, 0%) or puc (1/19, 5%) (p=0.04). Ten of these 13 patients with pseudo-progression were initially asymptomatic and three patients initially suffered from seizures but became symptom-free with anti-epileptic drugs. The patient with puc was initially asymptomatic and remained symptom-free during follow-up.
The rates of patients who suffered from continuing or worsening symptoms were not significantly different (p=0.47): 56% for patients with pseudo-progression, 51% for patients with tumor progression and 68% for patients with puc.

In 18/65 patients spontaneous regression of an initially pseudo-progressive lesion was observed. One of these 18 patients (mentioned above) experienced spontaneous neurologic improvement, five of them remained clinically stable without symptoms and 12 had stable or worse symptomatology.

Fig 3a shows the overall survival curves from the date of SRT of the patients with and without a progressive lesion. The median survival (IQR) and 1-year survival rate were 4.8 (2.1 – 9.7) months and 18% for patients without progression, 15.9 (9.5 – 30.5) months and 64% for patients with a pseudo-progressive lesion, 19.7 (14.8 – 23.9) months and 89% for patients with local tumor progression and 9.3 (5.1 – 13.4) months and 26% for patients with puc. The overall survival from SRT of the patients without progression was significantly worse compared to all patients with progression combined (p<0.001). The median survival rates from SRT of patients with pseudo-progression and tumor progression were not significantly different (15.9 versus 19.7 months; p=0.9).

Fig 3b shows the overall survival curves from the date of progression of the patients with lesion growth. The median survival (IQR) and 1-year survival rate from the date of progression of the patients with a pseudo-progressive lesion were 8.6 (4.2 – 20.5) months and 35%, of the patients with local tumor progression 13.3 (11.8 – 14.5) months and 56% and of the patients with puc 4.9 (1.8 – 6.7) months and 0%. The median survival rates after progression of patients with pseudo-progression and tumor progression were not significantly different (8.6 versus 13.3 months; p=0.7).

Table 2c shows the patients' causes of death. On the last follow-up date seven of the 37 pseudo-progressive patients (19%) were still alive, as well as one of the nine patients with tumor-progression (11%). The causes of death show a similar pattern in the three patient groups. The progressive lesion was the cause of death in 3/9 (33%) patients with tumor progression and was directly related to the cause of death in 5/37 (14%) patients with pseudo-progression (three patients died of complications of steroid use, one of progressive dementia and one of hemorrhage in the lesion).

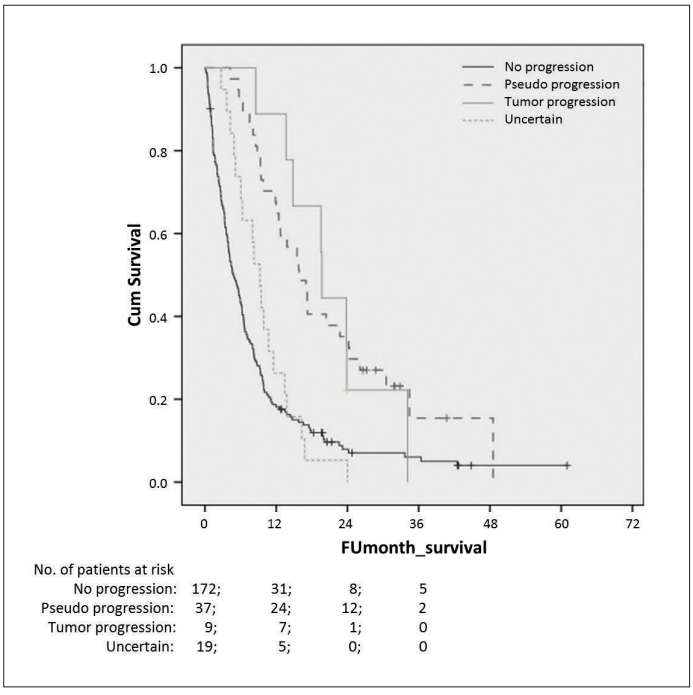

Figure 3a. The overall survival from the date of SRT of patients without progression, with a pseudo-progressive lesion, with local tumor progression and with a progressive lesion of uncertain cause.

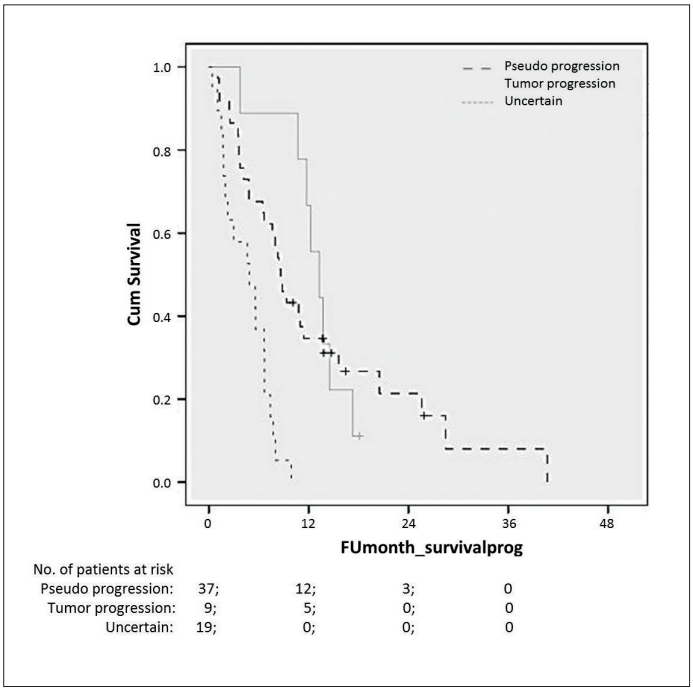

Figure 3b. The overall survival from the date of progression of the patients with a pseudo-progressive lesion, with local tumor progression and with a progressive lesion of uncertain cause.

DISCUSSION

In this study we described the clinical course in 65 patients with 84 growing lesions after SRT of brain metastases. In 57% (37/65) of these patients pseudo-progression was found to be the cause of the lesion growth. After initial lesion growth neurological improvement was found in 44% of patients with tumor progression (4/9, all had resection of the growing lesion), but in only 8% of the patients with pseudo-progression (3/37, one had surgery, one received corticosteroids and one had spontaneous improvement). However, 35% (13/37) of the patients with pseudo-progression remained free of neurological symptoms attributed to that lesion, in contrast to none of those with tumor progression. Neurological symptoms remained stable or worsened in 51% (19/37) and 56% (5/9) of the patients with pseudo-progression and tumor progression, respectively. We conclude that the clinical course of patients with symptomatic pseudo-progression is similar to that of patients with tumor progression, but that patients with asymptomatic pseudo-progression have a more favorable clinical course. Symptomatic pseudo-progression should therefore be regarded as serious radiation toxicity.

The main finding of this study is that the majority of pseudo-progressive lesions caused neurologic signs or symptoms that did not resolve spontaneously. The serious nature of symptomatic radiation induced necrosis of the brain is confirmed in only few published reports. The poor clinical prognosis in symptomatic patients was noted in a small study on post-SRT radiation necrosis, in which none of seven untreated patients showed any improvement of their neurologic symptoms 9. Moreover, 32% (56/174) of patients with temporal lobe necrosis after radiotherapy of nasopharynx carcinoma even developed grade 4 or 5 complications such as brain abscess, intracranial hemorrhage and sepsis [14].

Patients with a progressive lesion after SRT were found to have a better overall survival than patients without growth on MRI. Other authors also reported this finding 1. The most likely explanation for this counterintuitive result is that lesion growth can only be diagnosed if the patient's performance status allows for follow-up imaging. Therefore, lesion growth is diagnosed in a favorable selection of patients. Moreover, we found, as other authors did, that the survival of patients with pseudo-progression or tumor progression is similar [11]. Only a minority of the progressive lesions was related to the cause of death. This result confirms that the clinical course has no strong relation with the nature of the progression in patients with a growing lesion after SRT.

Our volumetric follow-up revealed spontaneous regression after the progression phase in 40% of the lesions. There are conflicting data in the SRT literature about the incidence of this secondary regression. Some authors consider absence of this regression as an indication of tumor recurrence [15]. In a volumetric follow-up study after SRT in 233 patients with brain metastases three types of volumetric response were distinguished, but a regression after progression pattern was not mentioned [16]. A regression rate comparable to the one in our study was reported in patients with pseudo-progression after SRT of brain metastases (57% at 1 year) and also in nasopharynx cancer patients with temporal lobe injury induced by fractionated radiotherapy (39%) [10, 17].

Spontaneous recovery of symptoms without treatment was only seen in one patient (with a pseudo-progressive lesion), but the majority of the patients in whom the progressive lesion was treated surgically experienced improvement of clinical signs or symptoms (83%, 5/6). Since spontaneous recovery of symptoms is rare, it seems that active treatment, if possible, should be preferred over observation in all patients with symptomatic growing lesions after SRT, irrespective of the cause of the progression. Asymptomatic lesions, on the other hand, can be observed without intervention. Guidelines for this clinical situation cannot be derived from the currently available literature. Some possible approaches for symptom management are suggested in the literature, including surgery, VEGF inhibition and laser ablation

[9, 18-12]. The most promising method comes from the earlier mentioned randomized study in patients with symptomatic pseudo progression, in which all patients who were treated with bevacizumab and none of the seven control patients showed improvement of neurologic symptoms [9].
In the progressive lesions for which no histological diagnosis was available and did not show spontaneous regression, our diagnosis relied on the interpretation of the perfusion MRI scans. Authors who only consider the volumetric follow-up or histology for characterization of post-SRT lesion growth diagnose tumor progression more often than pseudo-progression 17. The difference with our policy is that we did not regard continuing lesion enlargement as tumor progression by definition and did not rule out pseudo-progression if perfusion MRI showed no high rCBV. Studies about the use of perfusion MRI report a sensitivity of 70-91% and a specificity of 73-93% using rCBV maps. Consequently some uncertainty in a diagnosis that is based on perfusion MRI alone is unavoidable [11, 12]. Moreover, interobserver variability has been reported in the interpretation of perfusion MRI scans [21]. Therefore, we only considered a radiological diagnosis robust if there was agreement between the two neuro-radiologists. Nevertheless, the diagnosis remained uncertain in 19 of the 84 lesions (23%), because a reliable interpretation of the perfusion MRI was not possible, often due to susceptibility artifacts. This rate of non-conclusive perfusion MRIs is similar to the rate reported by Hoefnagels et al (19%) [11].

Our study has several limitations. First, the retrospective study design is susceptible to recall and reporting bias. Specific symptoms may not have been reported correctly and data of variables of interest may be missing. Another limitation is that the follow-up duration is different for all patients, also limited by the availability of MRI scans. This may have resulted in an underestimation of the percentage of patients with regression and/or symptom improvement; i.e., this may not have been detected because it occurred later in time. Moreover, the limited number of patients with definite pseudo-progression and tumor progression may have limited our ability to detect statistical differences. On the other hand, this patient population is representative for patients treated with SRT in an outpatient clinic, and our results are therefore valuable for clinical practice.
In conclusion we found that asymptomatic pseudo-progressive lesions after SRT of brain metastases have a relatively benign course and frequently remain asymptomatic. The clinical course of symptomatic progressive lesions is not so much determined by the cause of the progression. Spontaneous recovery of clinical symptoms caused by a pseudo-progressive lesion only rarely occurs, even if the lesion shows secondary regression. Therefore, symptomatic pseudo-progression is serious radiation induced toxicity, for which active treatment should be considered.

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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 cm^3). 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 BED_{12}, while protecting the normal brain due to a lower 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 20Gy 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 > 13cm^3 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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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 > 13cm^3 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 remained or became asymptomatic. We concluded that patients with symptomatic pseudo-progression or local tumor progression after SRT have a similar clinical course. However, patients with asymptomatic pseudo-progression have a more favorable clinical course, because they often remain asymptomatic.

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.

NEDERLANDSE SAMENVATTING

Stereotactische radiotherapie (SRT) is een belangrijke behandelingsmodaliteit voor patiënten met intracraniële tumoren. Het belangrijkste kenmerk van SRT is de hoge mate van nauwkeurigheid, die een zeer precieze en effectieve behandeling van tumoren mogelijk maakt en waarbij tegelijkertijd schade aan het kwetsbare omgevende hersenweefsel zoveel mogelijk vermeden wordt. In RCWEST begonnen we in 2004 met SRT op de Novalis, een voor de SRT aangepaste lineaire versneller. Kort daarna werd een SRT team opgericht. Daarin werden wekelijks technische en klinische problemen besproken die zich voordeden bij de introductie van SRT. De vragen die opkwamen tijdens deze discussies, vormden het beginpunt van dit onderzoek over SRT van intracraniële tumoren. In dit proefschrift worden zeven onderzoeken beschreven die gedaan werden met het doel de behandelingstechniek te optimaliseren en om meer inzicht te verkrijgen in de klinische effecten van SRT van hersenmetastasen.

Hoofdstuk 1 is een algemene inleiding. Hierin wordt de geschiedenis van SRT en radiochirurgie beschreven, alsmede de ontwikkeling tot de hedendaagse SRT. Radiochirurgie en SRT hebben vandaag de dag veel gemeenschappelijke kenmerken, maar de geschiedenis van radiochirurgie is heel anders dan die van SRT. Het idee van radiochirurgie is afkomstig van de Zweedse neurochirurg Leksell. Hij bevestigde een Röntgen buis aan een stereotactisch frame om met een hoge mate van nauwkeurigheid een letsel in de hersenen te kunnen aanbrengen door middel van een eenmalige hoge dosis straling. Deze methode om een weefselletsel in de hersenen te produceren werd als een chirurgische procedure beschouwd en werd daarom radiochirurgie genoemd. Sindsdien is de techniek van radiochirurgie verbeterd en werden er nieuwe indicaties voor ontwikkeld, zoals de behandeling van tumoren. Het basale idee van de neurochirurgen over radiochirurgie bleef echter hetzelfde, namelijk dat het een methode was voor het produceren van een weefselletsel door middel van een eenmalige hoge dosis straling. Na de uitvinding van de lineaire versneller en de ontwikkeling van radiotherapie als medisch specialisme werd het echter ook voor radiotherapeuten mogelijk om stereotactische behandelingen toe te passen. Radiotherapeuten hadden echter hun radiobiologische achtergrond en daardoor ervaring met gefractioneerde behandelingen. Zij beperkten zij zich dus niet tot eenmalige bestralingen, maar gingen ook de waarde van gefractioneerde stereotactische behandelingen onderzoeken. Aangezien velen van hen deze behandelingen beschouwden als een vorm van radiotherapie, introduceerden zij de term stereotactische radiotherapie. Tegenwoordig zijn er diverse technieken beschikbaar op het gebied van de stereotactische behandelingen. Het gebruik van een stereotactische frame is niet langer noodzakelijk, omdat beeld gestuurde radiotherapie even nauwkeurig kan zijn als behandeling op basis van een frame. Wij definiëren craniale SRT als een toepassing van uitwendige radiotherapie, waarbij een bestralingsdosis zeer nauwkeurig, op basis van lokalisatie met een stereotactisch frame of beeld gestuurd, in een of meerdere fracties wordt toegediend aan een intracranieel doelgebied. Wij beschouwen radiochirurgie en SRT met één fractie als equivalent.

Hoofdstuk 2 bestaat uit twee technische studies, die tot doel hebben de behandeling te optimaliseren.

Hoofdstuk 2a beschrijft de resultaten van een vergelijkende planningsstudie. SRT planningen werden gemaakt voor 25 patiënten met een glioom of meningeoom. Voor alle patiënten werden twee bestralingsplannen gemaakt, namelijk één Dynamic Conformal Arc (DCA) plan, dit is een "forward" geplande techniek, en één Intensity Modulated Radiation Therapy (IMRT) plan, een invers geplande techniek. De plannen werden geëvalueerd volgens een aantal tevoren vastgestelde criteria. Wij vonden dat acceptabele plannen mogelijk waren met zowel een DCA als met een IMRT techniek. Een voorkeur voor een DCA of een IMRT kon niet voorspeld worden aan de hand van tumor type, grootte of vorm. De voorkeur voor een van de twee technieken werd in sommige gevallen bepaald door verschillen in confor-

miteitsindex, homogeniteitsindex of de dosis in een kritieke structuur. In de meeste gevallen was er echter geen duidelijk verschil. Sindsdien geven we de voorkeur aan DCA bij de meeste craniale SRT patiënten, vanwege de kortere toedieningstijd en minder tijdrovende kwaliteitscontroles vergeleken met IMRT.

In hoofdstuk 2b worden de resultaten gerapporteerd van een onderzoek naar de fixatie van de patiënt tijdens SRT. Optimale fixatie van de patiënt is een essentiële voorwaarde voor een nauwkeurige toepassing van craniale SRT. Toen we het SRT programma opstartten, maakten we gebruik van het standaard niet-invasieve frame met het Brainlab masker systeem, waaraan een bovenkaakssteun (upper jaw support, UJS) werd bevestigd om de immobilisatie te verbeteren. Op basis van metingen met het Exactrac systeem van Brainlab concludeerden wij dat er nog ruimte voor verbetering van de fixatie was. Op onze afdeling werd een aanpassing voor het Brainlab masker systeem ontwikkeld, waarmee een vacuüm bijtblok (vacuum mouth piece, VMP) aan het frame bevestigd kon worden. In dit onderzoek vergeleken wij de nauwkeurigheid van de positionering voor en na behandeling bij 20 SRT patiënten die geïmmobiliseerd werden met de UJS met die van 20 SRT patiënten die geïmmobiliseerd werden met het VMP. Wij vonden dat gebruik van het VMP resulteerde in kleinere rotaties bij de instelling vóór de fractie en kleinere rotaties en translaties tijdens de bestralingsfractie. Nadat wij deze resultaten gevonden hadden gingen we het VMP gebruiken bij alle craniale SRT patiënten indien de dentitie dit toeliet en de UJS bij de overige patiënten.

Hoofdstuk 3 bestaat uit drie klinische studies over de resultaten van SRT bij patiënten met hersenmetastasen.

In hoofdstuk 3a worden de resultaten gerapporteerd van SRT in het eerste cohort van 86 patiënten met hersenmetastasen, die behandeld werden tussen juli 2004 en januari 2007 op onze Novalis lineaire versneller. De mediane overleving van de gehele groep patiënten was 6,2 maanden. Prognostische factoren voor de overleving waren de Karnofsky Performance Score (KPS) en het geslacht. De mediane overleving van patiënten met een KPS ≥90 en <90 was 9,5 maanden respectievelijk 3,9 maanden. Patiënten met een goede KPS hebben dus meer kans om lang genoeg te blijven leven om daadwerkelijk voordeel te hebben van SRT dan patiënten in minder goede conditie. Prognostische factoren voor lokale controle waren de KPS en de bestralingsdosis. Een belangrijke bevinding was het teleurstellende lokale controle percentage (37% na 12 maanden) bij grotere metastasen na 1 fractie van 15 Gy. In de discussie wordt besproken hoe de lokale controle verbeterd zou kunnen worden, namelijk met chirurgie of gefractioneerde stereotactische radiotherapie (FSRT). In dit patiënten cohort werden alleen conventionele MRI scans en FDG-PET scans gemaakt als radionecrose werd vermoed. Zo werd bij 6% van de bestraalde metastasen radionecrose tijdens de follow-up gediagnosticeerd.

We besloten vervolgens dat FSRT geïndiceerd was bij de grotere hersenmetastasen om de lokale controle te verbeteren. We kozen voor het 3x 8Gy schema, omdat het Biologically Equivalent Dose (BED) model suggereerde dat dit schema veilig zou zijn en mogelijk tot een betere lokale controle zou leiden. Tegelijkertijd besloten we een literatuur onderzoek te doen om bewijsmateriaal te verzamelen met betrekking tot de relatie tussen SRT dosis en de kans op lokale controle.

In hoofdstuk 3b wordt dit literatuuronderzoek beschreven. We bestudeerden de literatuur over de resultaten van SRT van hersenmetastasen, gepubliceerd van 1990 tot en met 2009. Uit slechts 11 van de 260 gepubliceerde artikelen kon een relatie tussen dosis en lokale controle afgeleid worden. In deze 11 artikelen vonden we dat de lokale controle na SRT in één fractie in sterke mate bepaald werd door de hoogte van de dosis. Het één-jaars lokale controle

percentage was hoger dan 80% als de dosis ≥ 21 Gy was, hoger dan 60% na een dosis ≥ 18 Gy en lager dan 50% na een dosis ≤ 15 Gy. Het één-jaars lokale controle percentage was 70% of hoger met alle gepubliceerde FSRT schema's en was ook hier afhankelijk van de hoogte van de dosis. Uit al deze gegevens konden we een BED afleiden die tenminste voorgeschreven zou moeten worden voor een één-jaars lokale controle percentage van 70%. Deze BED correspondeert met één fractie van 20 Gy, twee fracties van 11,6 Gy of drie fracties van 8,5 Gy. Het was niet mogelijk om conclusies te trekken betreffende een relatie tussen dosis, bestraald volume en de kans op radionecrose.

In hoofdstuk 3c worden de resultaten gerapporteerd van FSRT (3x 8Gy) in een tweede cohort patiënten, behandeld van september 2007 tot en met september 2009. In dit cohort waren alleen patiënten opgenomen die FSRT hadden ondergaan voor twee indicaties: metastasen met een PTV volume > 13cm^3 of metastasen in de hersenstam. De lokale controle percentages van deze patiënten werden retrospectief vergeleken met de resultaten bij de patiënten in het eerste cohort met dezelfde tumorkenmerken, die met 1x 15Gy behandeld waren. Met alle bekende tekortkomingen van een retrospectieve vergelijking en van de kleine patiënten aantallen werd de conclusie getrokken dat het 3x 8Gy schema niet duidelijk superieur was aan 1x 15Gy. Het één-jaars lokale controle percentage was lager dan 70% met beide schema's. Inmiddels was voor patiënten met een groeiende laesie na SRT de perfusie MRI beschikbaar gekomen, om het onderscheid te kunnen maken tussen tumor progressie en pseudo-progressie (een bestralingsletsel, waarvan de groei vaak slechts tijdelijk is). Na één-jaar waren de percentages pseudo-progressie niet significant verschillend na 15Gy (15%) of 24 Gy (25%). Wij concludeerden dat FSRT schema's met een hogere BED noodzakelijk zouden zijn om hoger lokale controle percentages te bereiken. Deze conclusie was in lijn met de conclusie in hoofdstuk 3b. De onderzoeken beschreven in hoofdstuk 3 riepen echter weer vragen op over de oorzaak en de incidentie van pseudoprogressie in deze patiënten groep.

Hoofdstuk 4 bestaat uit twee onderzoeken die zich speciaal richten op de groeiende laesie na SRT van hersenmetastasen.

Hoofdstuk 4a gaat over de aard van de pseudo-progressieve laesie. Dit hoofdstuk behandelt de vraag of de groei van de pseudo-progressieve laesie veroorzaakt wordt door volume toename van de bestraalde metastase of door aankleuring van het omgevende normale hersenweefsel. Om dit fenomeen beter te begrijpen hebben we filmpjes gemaakt van een serie achtereenvolgende met elkaar gefuseerde follow-up MRI scans. In deze filmpjes was telkens vrijwel dezelfde volgorde van veranderingen te zien in de 10 bestudeerde patiënten. We trokken de conclusie dat pseudo-progressie waarschijnlijk een effect van de bestraling is op het omgevende normale hersenweefsel en niet op de metastase zelf.

In hoofdstuk 4b wordt een onderzoek beschreven dat tot doel heeft de kliniek te beschrijven van patiënten met een groeiende laesie op basis van pseudo-progressie of tumor progressie. We bestudeerden het klinisch beloop van 65 patiënten met 85 groeiende laesies na SRT van een hersenmetastase. Bij de meerderheid van deze patiënten werd tijdens de follow-up ook een perfusie MRI scan gemaakt. Pseudo-progressie werd gediagnosticeerd in 59% en tumor progressie in 11% van de groeiende laesies; in 30% kon de oorzaak van de groei niet vastgesteld worden. Neurologische symptomen ontwikkelden zich bij 70% van de patiënten met pseudo-progressie en bij 100% van de patiënten met tumor progressie. Vier patiënten (44%) met tumor progressie verbeterden na resectie van de progressieve tumor. Vijfendertig procent van de patiënten met pseudo-progressie bleven asymptomatisch of werden dat. Van de patiënten met pseudo-progressie en tumorprogressie bleven bij respectievelijk 51% en 56% neurologische symptomen bestaan. We concludeerden dat het klinisch beloop bij patiënten

met symptomatische pseudo-progressie vergelijkbaar is met dat van patiënten met tumor progressie. Patiënten met asymptomatische pseudo-progressie hebben echter een gunstiger klinisch beloop, omdat zij vaak asymptomatisch blijven.

Hoofdstuk 5 bestaat uit een discussie van de belangrijkste bevindingen van dit proefschrift en een bespreking van ontwikkelingen die in de toekomst verwacht worden.

De twee technische studies gaan over radiotherapie planning en fixatie van de patiënt. Wij concludeerden dat acceptabele plannen gemaakt konden worden met DCA en IMRT. In moderne SRT kunnen echter geavanceerdere technieken toegepast worden, zoals volumetric modulated arc therapy (VMAT) en single isocenter dynamic conformal arcs (SIDCA). Het belangrijkste voordeel van deze nieuwe technieken is de kortere behandeltijd, vooral voor patiënten met multipele hersenmetastasen die SRT krijgen. De waarde van proton therapie in vergelijking met SRT met fotonen bij patiënten met intracraniële tumoren moet nog vastgesteld worden. Het belang van de fixatie van de patiënt zal niet veranderen, ook al zal de positionering steeds meer gebaseerd zijn op beeldvorming en zullen de behandeltijden korter worden. Daarom blijft het VMP een belangrijk hulpmiddel voor de fixatie van de patiënt.

De klinische onderzoeken gaan over de relatie tussen SRT dosis en lokale controle en over late radiotherapie effecten bij patiënten met hersenmetastasen. We hebben vastgesteld welke BED nodig is voor een lokale controle percentage na een jaar van tenminste 70%. We zijn er voldoende zeker van dat een eenmalige dosis van tenminste 20 Gy nodig is voor een voldoende hoge lokale controle kans, maar meer klinische resultaten zijn nodig ter bevestiging van onze voorspellingen over gefractioneerde schema's. We hebben gerapporteerd dat pseudo-progressie na SRT van hersenmetastasen irreversibele neurologische schade kan veroorzaken. Om de kans op pseudo-progressie te verkleinen moet de grootte van de CTV-PTV marge heroverwogen worden. Er zijn indicaties dat de lokale controle kans niet kleiner wordt als deze marge verkleind wordt, maar dat de kans op pseudo-progressie wel kleiner wordt. Het is van belang dat we in de nabije toekomst het dosisvoorschrift en de dosisdefinitie van SRT uniformeren. Meer patiënten met hersenmetastasen zullen in aanmerking komen voor SRT, te weten geselecteerde patiënten die zich presenteren met 4 tot 10 hersenmetastasen en patiënten die een irradicale resectie van hersenmetastasen hebben ondergaan. Tenslotte zijn argumenten genoemd, waarom de radiotherapeut betrokken moet zijn bij de follow-up van patiënten met hersenmetstasen.

CONCLUSIES

In dit proefschrift wordt aangetoond dat radiotherapie plannen voor SRT van intracraniale tumoren zowel met DCA als met IMRT optimaal zijn. De fixatie van de patiënt wordt beter als een vacuüm bijtblok bevestigd wordt aan het stereotactisch frame. Met SRT worden uitstekende lokale controle percentages bereikt bij patiënten met kleine hersenmetastasen. Een BED is bepaald die minimaal nodig is voor het bereiken van een lokale controle kans van 70% een jaar na SRT van grotere hersenmetastasen. Om deze BED veilig te kunnen toedienen is dan gefractioneerde SRT nodig. Groei van de laesie na SRT van een hersenmetastase kan veroorzaakt worden door een toxisch effect van radiotherapie op omliggend normaal hersenweefsel. Deze zogenaamde pseudo-progressie kan symptomatisch of asymptomatisch zijn. Het klinisch beloop van patiënten met symptomatische pseudo-progressie is niet minder ernstig dan dat van patiënten met tumorprogressie. Symptomatische pseudo-progressie moet dus beschouwd worden als ernstige door bestraling geïnduceerde toxiciteit. De kans op pseudo-progressie kan verkleind worden door SRT toe te passen zonder CTV-PTV marge. De radiotherapeut moet betrokken zijn bij de follow-up van patiënten met hersenmetstasen.

CURRICULUM VITAE

Ruud Wiggenraad was born on December 19th 1954 in The Hague. After graduating from the Lodewijk Makeblijde College in Rijswijk in 1972, he studied medicine at the Leiden University. In March 1980 he obtained his Medical Doctorate. From April until August 1980 he gained his first experience in radiation oncology as a resident at the department of radiotherapy of the Westeinde Hospital in The Hague (head Dr. G. Kok). From September 1980 until December 1981 he passed his military service as a resident at the department of neurology of the Military Hospital Dr. A. Mathijssen in Utrecht. After a residency in internal medicine at the University Hospital Utrecht he started his training in radiation oncology at the department of radiotherapy of the University Hospital Utrecht in October 1982 (Prof. Dr. H. van Peperzeel). In October 1986 he was registered as radiation oncologist. From October 1986 until December 1987 he was staff member at the department of radiotherapy of the Academic Medical Center in Amsterdam. From December 1987 on he is radiation oncologist at the department of radiotherapy of the Westeinde Hospital (presently called RCWEST). Research on this department eventually led to this thesis.

Ruud is married to Yvonne de Pagter and together they have three children, Fleur, Hans and Jeroen.

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