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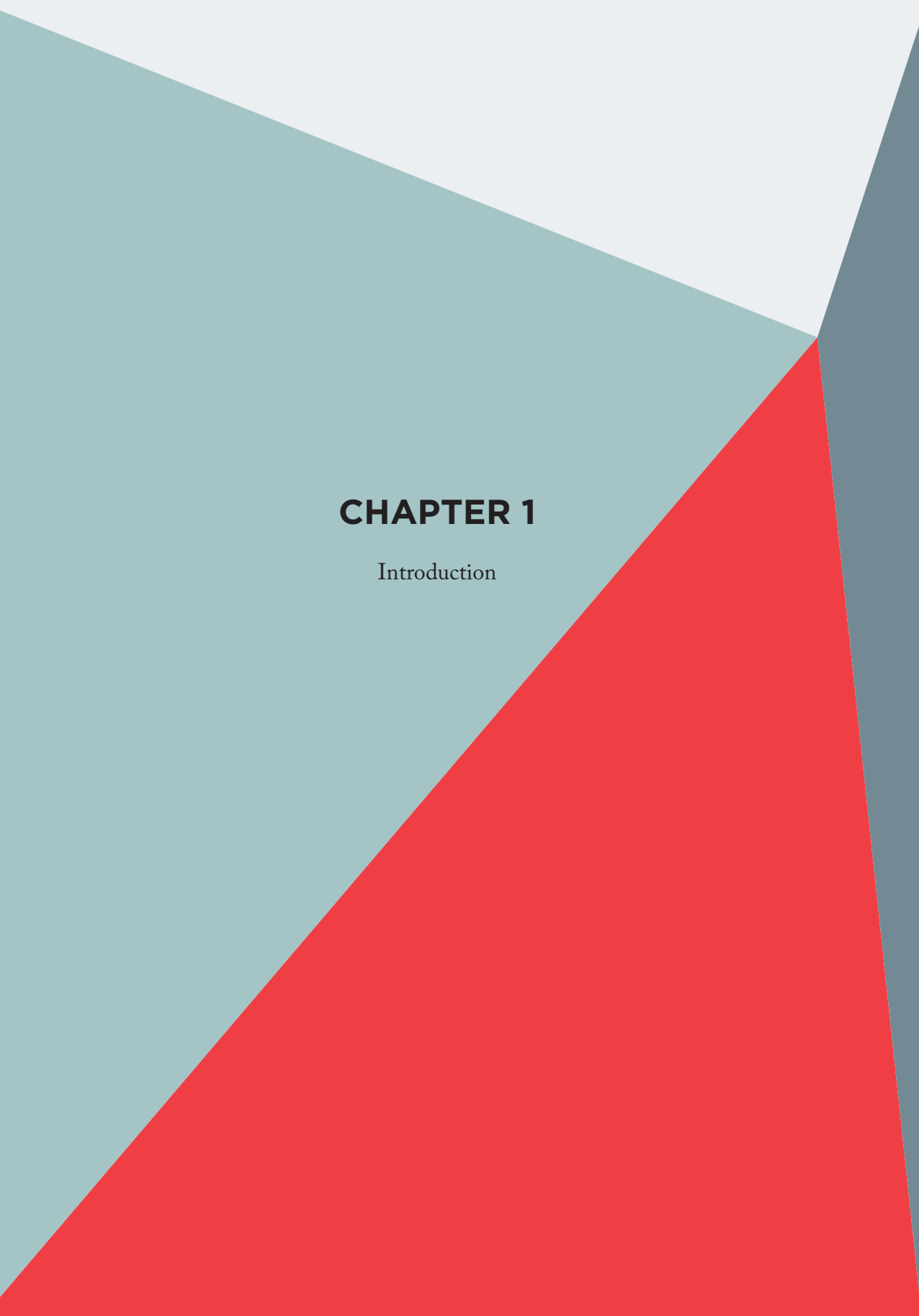


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CHAPTER 1

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. Horsley 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]. Leksell's 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 fractionation 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 been 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 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

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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 discuss 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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