Variability in target delineation in stereotactic radiosurgery with Leksell Gamma Knife® Perfexion™ and a perspective on radiobiological outcome: A multiobserver study

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Front page figure illustrates the workflow and purpose of the thesis, i.e. the target and dose distribution combined for the evaluation of the treatment outcome.
Conflict of interest

This study was performed in collaboration between Stockholm University and Elekta Instrument AB. Three of the supervisors are employed by Elekta Instrument AB.
Abstract

The use of stereotactic radiosurgery has increased significantly since the introduction in the 1960’s. With this technique the patient receives highly conformal dose distributions to the delineated target allowing the sparing of normal tissues and critical structures. Treatment success depends critically on the planning and therefore it is of interest to compare treatment planning strategies with respect to volume delineated, control of the tumor and risk of inducing stochastic and deterministic complications to the normal tissue. The purpose of this study is to quantify the multiobserver variability of target delineation for four brain disorders of a general complex nature and investigate the differences in radiobiological outcome. The four brain disorders, recurrent anaplastic astrocytoma, lateral frontal AVM, cavernous sinus meningioma and operated lateral vestibular schwannoma, were chosen because they are prone to present differences in the treatment volume and therefore the issue of accurate delineation is critical. They have all been treated with Leksell Gamma Knife® Perfexion™. Number of observers participating in this study is 20 and includes neurosurgeons, radiation oncologists and physicists chosen among those having high experience working with Leksell Gamma Knife® Perfexion™. The analysis of the delineated targets is based on a calculated average target structure which is assumed to resemble a true target if all observers delineate with the same clinical demands. The construction of this structure was shown to be highly influenced by the large differences in target volume which also influenced the statistical analysis of volume and radiobiological outcome. Conclusions are that differences between observers in target delineation for these four brain disorders appear to be clinically significant. A module allowing the evaluation of the plans from the radiobiological point of view for different target delineations was developed. The probability of controlling the tumour for the meningioma, astrocytoma and schwannoma, and the probability of AVM obliteration respectively were calculated based on the data available in the literature regarding their sensitivity to radiation. The invasive character into the normal tissue of the specific pathologies was also taken into account in the calculation of the tumour control probability. With respect to the irradiation of the normal tissue outside the target, the risk of developing a secondary cancer after stereotactic radiosurgery was also evaluated. This thesis presents thus the frame for dosimetric and radiobiological evaluation of the Leksell Gamma Knife® Perfexion™ plans taking into account the differences in delineating the target between various observers which has the potential of being a useful tool for clinical stereotactic radiosurgery.
ABBREVIATIONS

AVM – ArterioVenous Malformation
CI – Conformity Index
CCI – Concordance Index
CT – Computed Tomography
DCI – Discordance Index
DICOM – The Digital Imaging and Communications in Medicine
DVH – Dose Volume Histogram
LGK – Leksell Gamma Knife
LQ Model – Linear Quadratic Model
MRI – Magnetic Resonance Imaging
NTCP – Normal Tissue Complication Probability
OAR – Organs At Risk
PCI – Paddick Conformity Index
PET – Positron Emission Tomography
ROI – Region Of Interest
RT – Radiation Therapy
SRS – Stereotactic Radiosurgery
TCP – Tumor Control Probability
TPS – Treatment Planning System
1 INTRODUCTION

The Hippocratic Oath requires the physician to uphold a number of professional standards. Many medical schools have adopted modern versions that suit several of the professions in medicine, including that of the medical physicist as a part of the medical community. On short the oath states that the practitioners of medicine act for the cure of patients with honor and secrecy for the benefit of all patients.

The first performed surgeries were based on experience rather than knowledge. As we know today in medicine, the combination of theoretical and practical knowledge is vital for any occupation within this field. Before the evolution of theory, the knowledge was based solely on the practitioner’s experience for various conditions.

It is vital whenever ionizing radiation is used to stop the process of tumor growth, or any other abnormal pathological process, keeping the normal tissue and risk organs unharmed. This can be done in different ways; in conventional radiotherapy (RT) it is done by fractionation of the total dose and variable beam directions and field setups. The beams are angled to achieve high dose to target with the sparing of vital organs and surrounding normal tissue. Despite the effort to minimize dose to critical structures, there might still be a high cumulative dose delivered. Stereotactic radiosurgery (SRS) has in contrast the advantage of enhanced normal tissue sparing with the use of multiple focused radiation beams. In both RT and SRS, beams of ionizing radiation are used but the two techniques differ conceptually. Fractionated RT takes advantage of the difference in radiation sensitivity between normal tissue and pathological tissue, a difference which is not regarded in SRS. The ideal case, when prescribed dose conform to target with high dose gradients at the edge while sparing all normal tissue, is optimally achieved with radiosurgery. In SRS the volume of the target is usually smaller and the dose is delivered with high doses per fraction, while the number of fractions is often only one. This is achieved with high accuracy by using the radiosurgical equipment available today. Leksell Gamma Knife® Perfexion™ (LGK) is the equipment which constitutes the foundation of the evaluations in this study and the analysis is valid for older versions as well.

In the evaluation of radiosurgical plans, the treatment planner has a central role. Radiosurgeons, physicists, neurosurgeons and neuro-radiologists are all involved in this process. The users of this high precision method, such as the LGK, must be trained for the purpose of delivering high doses that conforms to the delineated volume. The process of constructing a plan usually begins with the initial delineation of target. The role of the planner is to create a plan where prescribed dose conforms to the delineated target volume, still keeping regions of healthy tissue, risk organs and potential microscopic spread in mind. In many cases a reasonable compromise for a particular
clinical case has to be found between the dose conformity to the target and the sparing of the normal tissue. Compromises may imply irradiating some amount of healthy tissue to be able to achieve target conformity, or reduce the dose to a part of the lesion to spare some nearby critical structure.

A high dependence of target volume on choice of imaging technique for treatment planning is shown and careful consideration must be taken to the pathology of interest. Effort should be made to select the most suitable imaging method, since improved target volume delineation can reduce the dose to normal tissue and improve tumor control. Developments of imaging techniques for treatment planning have refined the tumor delineation and the technique that is mainly used is magnetic resonance imaging (MRI). Imaging of soft tissue with MRI is superior in comparison to computed tomography (CT). On the other hand, CT has the advantage of providing information on electron density. This is important information for determining the absorbed dose. Since the brain has a rather homogenous composition that could be approximated as water, MRI could be used instead of CT for target delineation. Furthermore, parameters in MRI sequences can be adjusted for the visualization of alternate soft tissue contrast. This is advantageous in evaluation of the extent of tumor invasion in the normal tissue at the target edges which would enhance the accuracy of target delineation, (Khoo and Joon. 2006). Furthermore, artifacts produced in CT acquisition are avoided by the use of MR techniques resulting in more accurate target delineation (Webster et al. 2009). However, MRI is not a technique free of artifacts either (e.g. distortion) and sometimes planners use CT images when the geometrical artifacts present in MR images make planning difficult. The produced artifacts could result in a target localization error. For high grade gliomas it was shown that the inter-observer variability in target volume delineation based on CT and MRI co-registration was reduced compared to CT and MRI alone. (Cattaneo et al. 2005). Another study made on five patients with inoperable brain tumors showed a high inter-observer variability in gross tumor volume (GTV) delineation. This variability was as high on CT as on CT+MRI and the volumes were larger on CT+MRI (Weltens et al. 2001). Observers were asked to delineate the visible tumor spread without taking microscopic spread into consideration and the authors recommend the combination of the two image modalities for brain tumor delineation. This is another example of the importance of proper image studies. Emphasis has to be made to the inadequacies of imaging techniques as the basis for tumor delineation. When an observer plans for post surgery treatment it is also of high importance to evaluate the target position, shape and size on post surgical images. The danger of excluding the tumor progression after surgery when planning on pre-surgery images lies in the so called brain shift which occurs after surgery (Farace et al. 2011)

A further important issue with SRS with LGK, except choice of imaging technique, is the variation of parameters in treatment planning which provides flexibility for the treatment planner.
and may also give rise to the variation in treatment strategy, for one patient and pathology. Parameters that can be varied are number and weights of shots, position of shots and collimator sizes.

Planning strategy is also varying depending on pathology. In this thesis, four different pathologies are evaluated with respect to various delineation methods and the radiobiological response related to this variation is also evaluated. The pathologies are arteriovenous malformation (AVM), anaplastic astrocytoma, vestibular schwannoma and meningioma.

Koga et al. (2011) evaluated the influence of inter-operator differences, experience and radiographical technologies on the delineation and outcome for AVMs. Their analysis was based on 514 patients with AVM who underwent SRS. The result was that complete nidus obliteration\(^1\) was achieved in 72% of patients 3 years after SRS and in 89% of patients 5 years after SRS. All patients were treated with LGK. Another conclusion was that the experience of the operator was correlated to the morbidity. For large AVM’s, the overall morbidity was shown to be higher when the operator was less experienced. At the University of Pittsburgh Flickinger et al. (2003) evaluated complete AVM obliteration after Gamma Knife radiosurgery was studied in 351 patients between 1987 and 1997. Both treatment volume and dose varied and the documented obliteration in fraction of patients was 73% imaged with angiography and 86% with MRI alone at the follow-up.

Anaplastic Astrocytoma is a high grade glioma. Hall et al. (1995) found a median survival after radiosurgery of 11.8 months within 9 patients and Kondziolka et al. (1997) found a median survival of 31 months within 23 patients with astrocytoma. In other words, the results from studies varies due to the fact that there are several factors affecting survival as e.g. age, gender, tumor volume (Larson et al. 1996)

Vestibular Schwannomas are benign intracranial tumors and a challenge in treatment is the preservation of nearby critical structures, like facial nerves. Yomo et al. (2010) conducted a study in which they evaluated the dose planning with LGK Perfexion compared to previous model 4C, and results are improvements in dosimetric parameters, especially for large tumors. Many studies have been conducted with perspective on treatment outcome in vestibular schwannomas and results are varying. In a review by Murphy and Suh (2011) it was reported control rates for treatment with LGK radiosurgery between 81% and 100% in treatments carried out between 1969 and 1989, all with a perspective on hearing preservation, trigeminal neuropathy\(^2\) and facial nerve neuropathy. Linskey et al. (1990) studied 26 patients for 19 months after treatment with SRS and a decrease in tumor size was noted in 11 patients and the remainders were stopped in their growth. Régis et al.

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\(^1\) The complete erasure of the lesion treated.

\(^2\) Damage to nerve
(2004) evaluated the functional results of Gamma Knife radiosurgery of vestibular schwannomas. Their material was the first 1000 patients to be treated at Marseille Timone University Hospital and reported tumor control at last check up was 97%.

Investigation of safety and efficiency of SRS compared to fractionated stereotactic RT within 35 patients treated with SRS and 18 with fractionated stereotactic RT was in 2002 published by Lo et al. (2002). The patients had suffered from meningioma and endpoints were local control rate (LC), tumor control probability and cause specific survival (CSS). The results were showing no major difference in the 3-year CSS whereas recurrences were developed to a higher extent in patients treated with SRS. The discussion follows with a concern of radiobiological response. Due to the late effects in normal brain tissue with one fraction SRS where meningiomas are close to critical structures, fractionated stereotactic RT would be the most preferable choice of treatment. A study based on 99 patients 5-10 years following treatment with the LGK revealed a 93% tumor control rate and 63% of the tumors with a decreased size (Kondziolka et al. 1999). They recommend the use of Gamma Knife in the treatment of meningiomas provided that the tumor is not exceeding 3 cm in diameter which is the limitations of this technique. A study by Yamazaki et al. (2011) evaluated the inter-observer variability on stereotactic RT treatment for meningioma. Result showed that target volume delineated ranged between 6.04 and 14.5 cm³. The treatment was hypofractionated in five fractions with the CyberKnife system.

Apprehension of target delineation has been a concern in all areas of RT and no matter how optimal the choice of treatment modality may be there is still an observer who delineates the volume for treatment. Several studies have reported inter-observer variability in target delineation for example lung cancer (Giraud et al. 2002) and prostate/semi vesicles (Fiorino et al. 1998). There is however not much done dealing with inter-observer variability regarding LGK and in particular Perfexion.

The aim with this project is to evaluate the potential differences in target delineation and the radiobiological effect with respect to tumor control probability (TCP) and risk of secondary cancer in the normal brain. The fundamental data for this study is based on multi-institutional and multi-observer treatment planning on the same set of clinical data.

The radiobiological difference between conventional RT and SRS lies in the fractionation and dose delivery. In radiosurgery the aim is to completely arrest cell-division, no concern taken to the cells radiation sensitivity and oxygenation. In the treatment of highly malignant/infiltrative tumors, recurrences most always occur and in these cases conventional RT is often the first choice of treatment. Re-irradiation of recurrences due to the microscopic infiltration is limited for SRS due to the large cumulative dose to normal tissue received from conventional RT. The effect of the
infiltration on the normal tissue of meningioma, astrocytoma and vestibular schwannoma will be evaluated here from a radiobiological viewpoint assuming that outside the delineated target there are tumours cells that also have to be eradicated in order to prevent recurrences.

The radiobiological outcome from a treatment is dependent on the pattern of infiltration of the lesion treated. It is of key importance to design a treatment plan that takes the microscopic disease into account. This thesis will evaluate the outcome with an assumption of infiltration outside the border of target volume delineated. A study by Yamahara et al. (2010) focused on cell infiltration in the periphery of glioblastoma multiforme (GBM) where MR images are compared to findings from pathology analysis after autopsy in 7 patients. Reported areas with detected tumor cells extend 6-14 mm outside tumor boundary. Pirzkall et al. (2002) reported the validity of magnetic resonance spectroscopy (MRSI) in defining the extent of glioma infiltration. They suggest an addition of 2-3 cm margin to the clinical target volume (CTV). In another study by the same group they also suggest a nonuniform margin to assess tumor infiltration in evaluation of residual disease between surgery and RT (Pirzkall et al. 2004). The spread of tumor cells in the tissues surrounding visually seen target is poorly detectable and requires more advanced imaging techniques to identify the metabolically active tumor cells (Farace et al. 2011, Narayana et al. 2007). The areas in the proximity of the prescribed dose volume receive an absorbed dose that is dependent on the dose fall-off surrounding the target. A lower dose fall-off could be advantageous when suspicious microscopic spread is taken into account.

With respect to the normal tissue and the risk of developing secondary cancer after radiosurgery as pointed out by Dasu et al. (2005), most of the available dose-response models are valid for low doses/low dose-rates and cannot easily be extended to SRS. Linear or non-linear models are both available and the difference in the latter is the consideration of the competition between induction of carcinogenic mutation and the cellular survival for risk calculation. Linear models assume a linear relationship between dose and risk of secondary cancer following RT. In the study by Dasu et al. (2005), methods for calculating the risk of cancer induction following RT are analyzed. Conclusions were that the linear risk model is inappropriate in this calculation and the competition of cell kill versus DNA mutation induction has to be taken into consideration. The complete approach in risk estimation is undertaken by the use of competition risk models and the full dose distribution. In radiosurgery the target is defined with no extra margin. This is advantageous with respect to the normal tissue from the radiobiological point of view. Smaller volumes of normal tissue can withstand higher doses of radiation than larger volumes and in radiosurgery the aim is that no volume of normal tissue should be irradiated with the prescribed dose to the tumor. Also, the target tissue affects the probability of a radiation induced reaction. This statement is based on a
comparison by Flickinger et al. (2003) where they looked at the post-radiosurgery imaging changes in AVM’s and meningioma. The probability of developing these changes was 7.5 times higher in AVM’s than for meningioma. This can be translated to the risk enhancement of normal tissue due to the effects in target vasculature; otherwise the risks should be the same for the same volumes irradiated with the same doses. Flickinger et al. (2003) showed that fast responding tumors such as glioblastoma multiforme display a good response to radiosurgery despite what their radiation sensitivity to fractionation suggests. This can be translated into the impact of tumor vasculature which is a late responding tissue. This is a factor that needs to be accounted for in the evaluation of tumor and normal tissues exposed to ionizing radiation. The primary target responding to radiosurgery was studied by Szeifert et al. (2002) and the results indicated that the vascular endothelium may be the primary target.

This thesis presents thus the frame for dosimetric and radiobiological evaluation of the Leksell Gamma Knife® Perfexion™ plans taking into account the differences in delineating the target between various observers which has the potential of being a useful tool for clinical stereotactic radiosurgery.
2 BACKGROUND

2.1 GAMMA KNIFE® PERFEXION™
LGK radiosurgery is a stereotactic method developed for patients unable to undergo conventional surgery (craniotomy) or conventional RT. When previously treated with the latter which gives a large cumulative dose to a large volume of normal brain, repeated treatment with the same modality is unsuitable due to normal tissue radiation tolerance. Craniotomy is not the appropriate method when dealing with lesions in the deeper parts of the brain or in the vicinity of OAR as the entire volume of the brain is often considered as one critical structure. LGK surgery is often performed in treatment of recurrences when conventional RT has been delivered in previous treatment sessions.

Lesions treated can be primary tumors, AVM’s, metastasis and functional targets like trigeminal neuralgia among others.

2.1.1 HISTORY OF RADIOSURGERY
Radiosurgery was initially developed by a Swedish neurosurgeon named Lars Leksell together with Professor Börje Larsson between 1950 and 1960 and at first the pathologies for treatment were functional diseases originating in the brain. The first stereotactic gamma unit using Co⁶⁰, was installed at Sophiahemmet Hospital in Stockholm 1968. The usage of this treatment facility was mainly for functional brain surgery, some tumors and AVM’s. A second unit was installed few years later, in 1978 at Karolinska Hospital in Stockholm. The word “radiosurgery” was coined by Leksell to visualize the annihilation of tumor tissue, giving a precise high dose in relation to conventional RT so with a method just as accurate as open skull surgery. The difference from conventional surgery, so called microsurgery or craniotomy, and radiosurgery is that there is no physical removal of target but the exposure to a high and conformal dose of ionizing radiation. The object of the two techniques remains the same; the complete destruction of target function.

Localization of target has been the main concern regarding the accuracy of radiosurgery and the reason of slow development. The initial basis for treatment planning and target localization was plain radiographs and the revolution came with the introduction of CT and MRI (Leksell, 1983). CT images provide electron density information which is necessary in dose calculations but has limitations regarding soft tissue contrast. Cellular abnormalities in soft tissue are better visualized in MRI images. The physical properties of MRI offered a solution to the problem of postoperative visualization of brain lesions. MRI was shown to be a valuable tool and made SRS safer and more effective (Leksell et al. 1985, Khoo and Joon 2006).

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3 Characterized by intense pain in the face, originating from the trigeminal nerve
A few years later Gamma Knife radiosurgery was shown to be a good method to surgical resection and also provides a rapid palliative treatment of symptoms due to recurrent malignant tumors. Today it is one method for adjuvant treatment of primary malignant tumors for which the prognosis is poor together with the treatment of metastases, functional diseases and benign tumors. The number of units installed globally was over 250 in 2007 and the number of patients to undergo Gamma Knife surgery was almost 500,000 in 2006.

The newest model, Leksell Gamma Knife® PERFEXION™, was introduced by Elekta Instrument, AB, Sweden, in 2006. The apparatus is illustrated in Figure 1. The treatment and setup of patient is much more efficient with this model than with the previous since it is entirely automated. Régis et al. (2009) have reported minimal amount of patient-apparatus collisions, improved radiation protection and reduced time for intervention and quality assurance with this model compared to the previous model 4C.

![Image](image.png)

Figure 1. Leksell Gamma Knife® Perfexion™, illustration provided by Elekta AB.

### 2.1.2 PRINCIPLES OF GAMMA KNIFE® PERFEXION™

The Gamma Knife® Perfexion™ uses 192 $^{60}$Co sources distributed in 8 sectors and they are cylindrically arranged in five rings. Each sector has the capability of moving independently along the surface of the collimator. This specific feature is a chain in the evolution of Gamma Knife systems and is one of the characteristics of LGP Perfexion. The construction of treatment plans using hybrid shots is now possible, meaning that one shot consists of different collimator sizes in different sectors. A study by Petti et al. (2008) evaluates this use of independent moving collimator
sectors for the treatment of lesions close to critical structures and the unique dose fall-off characteristics of the hybrid shots. Their result was a reduction of the beam-on time meaning that the same treatments are performed within a shorter amount of treatment time. The 120 mm thick collimator body is made of tungsten and replaces the multiple helmets, primary and secondary collimators in previous models. Three collimator sizes are available, 4 mm, 8 mm and 16 mm. Previous models had 14 mm and 18 mm collimator sizes and they are now replaced with the 16 mm collimator size. Sectors can automatically be changed between collimator sizes without physician intervention. A sector mechanism positions the sources during treatment and also withdraws them into standby position between treatments. Each sector can also be placed in between two rows of the collimator, also referred as source plugging or sector blocking. The main function of this is to improve the dose fall-off along one direction from the target outline close to some critical structure. This improves sparing of this structure and is also applied to prevent individual beams from crossing a normal structure sensitive to any amount of radiation, (Ma et al. 2008). Perfexion also has an option called dynamic shaping which replaced the plug patterns in the previous models of LGK. It automatically blocks specified sectors to enable rapid dose fall-off close to critical structures. Automatic changes of collimator sizes according to treatment plan enable treatment times that are radically reduced. The treatable volume in LGK Perfexion is also increased compared to previous models, making it possible to treat multiple, peripheral and deep seated lesions with high accuracy and no risk of patient and collimator collision.

During the treatment procedure, 192 radiation beams converge on the target with high accuracy. The absorbed dose at isocenter becomes extremely high. This makes treatment planning ever so important in its accuracy. Elekta Instrument AB, Gamma Knife Perfexion ensures a target precision of 0.5 mm and this makes the treatment of pathologies closely surrounded by critical structures possible. Factors that could interfere with the target precision is for example the co-registration of images and possible image artifacts. The sections of radiation sources can be weighted by different collimators, different beam-on times to achieve non-spherical dose distributions. An amount of so-called spherical and elliptical “shots” creates the combined dose distribution of the target and can be used for highly non-spherical targets with satisfying results. Some of the hybrid shots also have a much more complex shape than just spherical or elliptical. A single shot results in a spherical or elliptical isodose distribution.

The head must be positioned with high precision to ensure complete accuracy with the focal point of collimated radiation sources. The patient’s head is placed in a stereotactic frame by the means of screws into the shallow part of the skull. This is the invasive part of radiosurgery today and is in no way comparable with the open craniotomy. Advantage with the stereotactic frame is
that the coordinate system is fixed to the patient and is literally the same both in imaging and during
treatment. Basis for treatment planning is an MRI acquisition sequence done with the stereotactic
frame in place. It constitutes a three dimensional coordinate system for the cranium and these
coordinates automatically specify how the patient is to be placed in the treatment unit. A treatment
plan is made with these coordinates as a reference system. In the treatment planning phase, the MRI
sequence with frame coordinates may be co-registered with other imaging techniques acquisitions
such as CT, PET (Positron Emission Tomography) and more advanced MRI sequences such as
FLAIR (Fluid Attenuated Inversion Recovery) which have been taken within a reasonable time
before treatment. This is due to the rapid growth of some pathology such as meningioma with
malignant appearance and anaplastic astrocytoma among others.

2.1.3 LEKSELL GAMMA PLAN
The treatment planning system for LGK is called Leksell GammaPlan (LGP). Latest version is
GammaPlan 10.0 and it connects the user with a highly user friendly work system, as shown in
Figure 2. Frameless image studies are fully supported meaning that the user can co-register image
sequences without frame to that acquired at the day of treatment with the stereotactic frame in
place. This feature is called ImageMerge add-on. It allows the observer to co-register images from
multiple sets of image sequences. Examples of these are both basic sequences (e.g. MRI-T1, MRI-
T2) and more advanced sequences (e.g. MRI-FLAIR, PET). The algorithm used for dose
calculations considers the patient equivalent to water, implying no tissue attenuation inhomogeneity
corrections (Beck and Berndt 2004). The treatment planning system (TPS) represents the dose
distribution for the lesion treated within a matrix that is defined surrounding the target. The size of
this matrix is set by the observer and contains 31x31x31 points where the relative dose is given
after calculated. This implies that a smaller matrix results in a more accurate 3D dose distribution
after exporting from LGP. The values within this matrix are relative a scaling factor given in the
DICOM (Digital Imaging and Communication in Medicine) header of the dose file.

A critical aspect of radiosurgery is the dose planning. The methods applied by the planner or
neurosurgeon differ but the priorities remains the same. Priorities are chosen by the treatment
planner and the first is often conformal coverage of target volume. Nerves that are located in the
vicinity of the target are then given next priority; facial, cochlear and trigeminal nerves are the main
nerves that could set the limit to target coverage. Another consideration must be taken to large or
central tumors where the brainstem is a critical structure (Niranjan and Flickinger 2008). The brain
consists as well of several other critical structures that must be taken into consideration in the
planning, like the whole optic apparatus. The observers study the dose volume histograms (DVHs)
for the critical structures to determine if the plans result in an absorbed dose lower than the limit for
each critical structure. A radiosurgical plan is constructed using the three dimensional coordinates from the stereotactic frame. These coordinates tells the Gamma Knife system where exactly to find the target and critical structures delineated by the planner. The planner specifies the site where the radiation is to be focused by placing shots. The final plan is a specification of many shots and end result is a prescribed dose distribution conformal to the target. It can be of high complexity by the combination of shots with different sizes and weights i.e. beam-on time. The latter is a main reason for the limitations on the complexity of the plan. It is not unusual that the treatment time exceeds one or several hours and the patient’s physiology must determine how far the planner can prolong the treatment time.

Figure 2. Leksell GammaPlan. Screen-shot illustrating the treatment planning system.

2.2 BRAIN DISORDERS
The brain disorders treated with SRS that made the subject of the analysis in this project were anaplastic astrocytoma, meningioma, vestibular schwannoma and AVM.
2.2.1 ANAPLASTIC ASTROCYTOMA
Anaplastic astrocytoma is a grade III (WHO\textsuperscript{4}) malignant glioma. These high grade tumors occur without identification of environmental risk factors and are usually centered in the deep white matter of the cerebral hemispheres. Most symptoms are produced due to the increased intracranial pressure of the enlargement of these tumors (Larson et al. 2002, Kaye and Laws Jr 2001). First choice of treatment is surgical resection, if the location of lesion permits this, followed by fractionated RT and chemotherapy. Gliomas are infiltrative tumors which limit the ability for surgical intervention (Combs et al. 2007). Re-irradiation of recurrent high malignant glioma is limited by the tolerance of surrounding normal tissue. Thereby, treatment options for recurrences are also limited to SRS which minimizes the dose to the critical structures surrounding the lesion. Prognosis of patients with this diagnose is poor and long term survival limited to only a fraction of patients. Reported median survival is rather variable but in most cases limited to one year (Voldermark et al. 2005, Salford et al. 1988). Recurrences are common due to the infiltrative character of this brain disorder.

2.2.2 MENINGIOMA
Meningiomas grow from the meninges, the layers of membranes covering the brain and spinal cord. Surgical resection may result in high rate of complications and morbidity depending on location. The cavernous sinus is a common location for this type of lesion and surgical resection in this case is correlated with a high probability of complications and morbidity. The tumor can be localized close to the optic apparatus and this tissue is highly radiation intolerant. In this case, localization sets the limit to the choice of treatment options. An aggressive surgical removal of tumors located at cavernous sinus or its proximity, ensures a worsening of optic nerve function or total loss (Newman 2007). The cranial nerves passing through the cavernous sinus can tolerate radiation higher doses than the optic nerves which are considerably more radiation sensitive (Tishler et al. 1993, Leber et al. 1998). Meningiomas are usually benign and the symptoms are not tumour specific and not always present at the point of diagnosis.

2.2.3 VESTIBULAR SCHWANNOMA
Vestibular schwannoma is a tumor of the nerve connecting the ear to the brain, also termed acoustic neuroma. It is slow growing, not life threatening but can cause damage to nerves involved in hearing, movement and feeling in the face. They grow from the myelin forming cells that cover the eighth cranial nerve. Watchful waiting is one approach in the management of vestibular schwannomas and clinical studies of their growth rate gives the approval of this (Modugno et al. 1998).

\textsuperscript{4} World Health Organisation
Treatment options involve surgical resection, RT and observation as a first option. Regardless of treatment, critical structure endpoint is the preservation of cranial nerves involved such as the facial and cochlear nerve and the brainstem. Because of the location of the vestibular schwannomas, the close proximity of critical structures, treatment of these lesions with SRS is a major challenge for the treatment planner and requires a meticulous dose distribution. Both the facial and the cochlear nerve generally courses along the lesion, the plan must be highly conformal in these regions (Niranjan and Flickinger 2008).

2.2.4 AVM
AVM is an abnormal connection between veins and arteries due to deficiencies of the cardiovascular system. Arteries distribute oxygen rich blood and veins carry oxygen-depleted blood back to the lungs and AVM’s interfere with the process of oxygen, nutrient and waste exchange in the capillary bed (Al-Shahi and Warlow 2001). SRS is an established treatment option in the management of AVMs in the brain. The risk of hemorrhage are minimized with the risk increasing with deeper seated lesions (Javalkar et al. 2009). The technique of SRS produces vascular injury that is conformal to the AVM nidus5 and is eventually leading to complete obliteration. This, together with limiting the probability of normal tissue complication is the aim of the SRS treatment (Yamamoto et al. 1995, Friedman et al. 1995). At the time of diagnosis, many patients are asymptomatic (about 15%) the rest having seizures together with the most common observed symptom which is intracranial hemorrhage (Al-Shahi and Warlow 2001). When the volume of the AVM increases, so does the probability of normal tissue complication. The progress of AVM obliteration is showed to be influenced by a number of parameters such as dose to the nidus, volume treated, location of the AVM and possibly the patient’s age. Complication of treatment is influenced by the presence of hemorrhage (Mavroidis et al. 2002).

2.3 RADIobiology of radiosurgery
The tolerance dose of the irradiated normal tissue is one of the limiting factors for the dose delivered to the target in all techniques of RT. In radiosurgery, the physician does not attempt to spare some tissues within the target and treat others, instead to achieve a complete destructive effect within the target volume while sparing all surrounding tissues.

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5 Nidus is latin for nest.
2.3.1 RADIOBIOLOGICAL MODELS FOR RADIATION CELL SURVIVAL AND THE ISSUE OF RADIATION SENSITIVITY

The cell survival or cell death is used in this context in the sense that cells have retained their reproductive integrity and are able to proliferate indefinitely or the complete loss of reproductive integrity also called reproductive death.

The most used model for cell survival is the Linear Quadratic model (LQ-model). This model is based on the assumption of two components to cell kill by radiation. One component is proportional to dose and the other is proportional to the square of dose. The linear and quadratic components are equal at a dose equal to the ratio of these two components and give the $\alpha/\beta$ ratio. Equation 1 gives the standard formula for the LQ model. For high doses delivered in one single fraction and high dose rates no account is taken to the repopulation and repair for most benign tumors. For malignant, fast growing tumors on the other hand it can be favorable to add a component related to repopulation in the general LQ formula (Niranjan and Flickinger 2008). Figure 3 illustrates the shape of the cell survival curve described using the LQ model and its parameters.

The model fits experimental data well in a fractionation scheme of 2 Gy fractions (Barendsen 1982). However, in the LQ-model, the exponential function leads to a continuous bending down of the curve which would suggest a lower survival fraction at higher doses. The data used for the fit of the LQ model are for doses below the doses used in SRS. However, experimental data have shown a linear relationship between the logarithmic values of survival fraction and the dose at high doses per fraction. This could yield an underestimation of the effect in relative survival fraction and hence would result in the need of a modified prediction model concerned with the linear relationship at higher single fraction doses (Puck and Marcus 1956, Park et al. 2008, Lind et al. 2003).

\[ SF = e^{-\alpha D - \beta D^2} \] (1)
Effects of radiation are divided into early and late, according to their response to fractionation. Tissues with a late response to ionizing radiation are more sensitive to fractionation or changes in this than early responding tissues. Early effects are the result of a large number of cell deaths within a short period of time. Late effects occur predominantly in slowly proliferating tissues such as the brain and central nervous system. The $\alpha/\beta$ ratio is a measure of the radiation sensitivity to fractionation of tissues. A low $\alpha/\beta$ ratio is the result of a slowly proliferating tissue such as the neurological tissues of the brain. Tumors often have a higher value because they proliferate more rapidly. Fractionation is in many cases beneficial in the treatment of some tumors. Other tumors that are centered in the brain have a lower $\alpha/\beta$ ratio and a fractionated treatment is not beneficial.

The response of a tissue to radiation depends on three primary factors; (1) the inherent sensitivity of individual cells, (2) the kinetics of the tissue and (3) the organization of cells in that tissue (Hall and Giaccia 2006). Tumors occurring in the brain evolve from different normal tissues and the radiation sensitivity depends largely on these tissues. The vascularization of these lesions and the oxygenation state of them has a large impact on their sensitivity as well. Regarding the cells of the brain, three major types are involved; neurons, vascular endothelial cells and glial cells. Neurons are nonproliferating cells, glial cells have a small stem-cell compartment with a slow repair function and endothelial cells can proliferate rapidly after injury. All the important radiation effects in the brain are late occurring tissue (Hall and Giaccia 2006). For late effects, as for the brain, the $\alpha/\beta$ is low meaning that the beta component has an influence at low doses. The $\alpha/\beta$ value for tumors is not higher than that for normal tissues in all cases. This can be translated into the interpretation that a
fractionation scheme is not regarded as advantageous with respect to normal tissue tolerance in all treatments. Since the fractionation methods take advantage of the difference in radiation sensitivity of normal tissue versus tumor tissue, if there is no major difference in the α/β value between lesion treated and the normal brain tissue no gain in treatment response is achieved with fractionation. Meningiomas and schwannomas are two of these brain disorders which are rather treated with SRS for a better treatment result (Kondziolka et al. 2007). AVMs are benign late responding tissues which indicate that nothing gained with fractionation in these brain disorders either. Anaplastic astrocytoma on the other hand is a brain disease with a rapid radiobiological response to ionizing radiation and a fractionation scheme might be favorable.

Larson et al. (1993) defined four categories for targets treated with a radiosurgical approach. Category 1 included a late responding target embedded within a late responding tissue, e.g. AVM. Due to the equality in response with respect to fractionation of both normal and target tissue, no advantage is achieved with fractionation of total dose. Here a surgical resection of target or SRS is the most favorable approach. Category 2 is stated as a late responding tissue surrounded by late responding normal tissue, e.g. meningioma. The treatment of this is the same as for AVM and an equivalent advantage in fractionation as for category 1. Meningioma is considered radiation resistant to doses within the range of fractionated radiotherapy (Kondziolka et al. 2007). In category 3, an early responding target is embedded within a late responding normal tissue. Astrocytoma as a target structure contains both normal cells and malignant cells and often invades normal tissue outside visible target boundary and belongs to category 3. Sparing of normal tissues within target could be achieved through fractionation. Category 4 included early responding target tissue surrounded by late responding normal tissue. Schwannomas are as well considered radiation resistant to doses in the range of fractionated radiotherapy (Kondziolka et al. 2007).

One limitation of the LQ model is that it works for doses employed by conventional fractionated radiation therapy. For higher doses per fraction as used in SRS the LQ model is less accurate.

Several other alternative models for radiation cell kill have been proposed in the literature in order to overcome the limitations of the LQ model to accurately describe the survival of cells at high doses per fraction. One of them which might have potential of being used in SRS is the repairable-conditionally repairable model (RCR model) proposed by Lind et al. (2003). In this model the response to radiation is described based on the assumption that there are two types of radiation damages, potentially repairable damages which could lead to cell death if unrepaired or misrepaired, and the conditionally repairable, which could be repaired or could lead to cell kill if not repaired correctly. Both types of damage follow Poisson statistics. The expression for survival is
given by Equation 2. The first term describes survival of undamaged cells and second term describes survival after sublethal damage repair.

\[ S(D) = e^{-aD} + bD e^{-cD} \]  

(2)

Although the RCR model might work better than the LQ model for the dose range used in SRS, the model has not been used in the present study due to the difficulties of finding or deriving the necessary parameters describing the clinical response of the brain disorders investigated in this study.

### 2.3.2 DOSE RESPONSE CURVES AND THE THERAPEUTIC WINDOW

A dose response curve describes the relationship between the radiation dose and the proportion of cells that survive resulting in a specific outcome. A typical set of dose-response curves giving the probability of controlling the target and the probability of inducing complications in the normal tissue as a function of the dose is illustrated in Figure 4. By optimizing the treatment, the two response curves for the target and for the normal tissue are pushed away and hence the therapeutic window width is increased. By the reduction of the margin of the target, the complication curve is shifted towards higher doses and therefore the therapeutic window is increased. The parameters D50 and γ gives the dose at 50% control of the target and the steepest slope of the dose-response curve.

Figure 4. Illustration of typical dose-response curves and therapeutic window.
2.3.3 RISK OF SECONDARY CANCER

Exposure of healthy tissues to low doses implies a risk of cancer and this is of the highest importance in younger patients (Epstein et al. 1997). That is due to the patient’s lifetime expectancy versus radiation induced effect. Cells that are mutated after RT must follow malignant cell division progression and result into tumors. Cells exposed to the therapeutic doses of Gamma Knife RT have negligible probability of mutation into malignant cells (Lindsay et al. 2001). Normal tissues surrounding the areas of high doses on the other hand receive low doses and are at the risk of malignant progression. For older patients the risk of developing secondary cancer is not as critical as for younger patients due to the time span of malignant progression.

2.4 DICOM

The Digital Imaging and Communications in Medicine (DICOM) is now implemented as the standard for diagnostic imaging. The DICOM-RT objects are all an extension of the DICOM standard.

The DICOM format makes sharing between different systems possible, thus the ability to make use of diagnostic images from different modalities in the treatment planning (Law and Liu 2009). In the TPS LGP the DICOM-export of treatment data results in RT dose-files, RT Structure set-files, one RT Plan-file and a set of Image-files. DICOM-RT enables the use of data from various treatment planning systems and image acquisition methods together with ImageMerge. Together with ColorPET it can be used to evaluate treatment planning options and post-treatment evaluation. The latter makes the use of PET images in the pre- and –post treatment evaluation possible.

2.4.1 RT DOSE

Absorbed dose is represented by isodose lines and can be visualized in Gy or percentage of maximum dose in LGP. RT-Dose file contains this information in the form of 2D dose planes combined to form a 3D structure. In the LGP planning process the observer sets a target matrix covering the target structures, this has always the size 31x31x31 and the resolution of this depends on the size of target structure. Several matrices can be used if the plan involves multiple targets or one complex target structure. While planning, the structures are delineated on a combined set of image modalities and the resulting target structure is often the union of several structures depending on the number of imaging techniques needed for planning. When exporting to DICOM files one receives one RT Dose-file for each structure, one for the target matrix and one for the skull. The observer can choose which matrices to export. Various methods of defining the target are present; the observer can set one target matrix or several for one target. The dependence on the number of
matrices is on the structure of target. With several matrices for one target the plan could be optimized if the target is large or of a complex shape. The values within the dose matrix are relative values; in the DICOM header of the RT-Dose file a tag called “DoseScalingFactor” is found. By multiplying each value within the dose matrix with this factor they are converted into Gy.

2.4.2 RT STRUCTURE SET
The RT-SS file defines a set of structures given in the treatment planning process as delineated target or targets, organs at risk and skull contour. It can be obtained from structure images such as MR, PET and CT. In the process of retrieving target outlines all coordinates are found within the RT-SS file. They are given as a large vector with x, y and z values. These can be visualized in slice planes and summed to a 3D plot. All slice planes are then associated with their respective z-coordinate. Identification of interslice distances is calculated by knowing the z-coordinates. In the DICOM export the observer can choose one image sequence together with structures- and dose files.

2.4.3 RT PLAN
Information on treatment plan is all found in the RT Plan-file. Only textual information is displayed here as the patient setup, beam setup, dose prescription and beam weighting.

2.4.4 RT IMAGE
In the treatment planning process, the observer chooses from various image-sets for the optimal structure and dose settings except for the AVM where it is not possible to export the angiography images. Their purpose is exclusively to work as guidelines for the delineation of the AVM target. While exporting the data for analysis and comparison there is as well a choice of the same image-sets. RT Image file consists of attributes of the image modality used i.e. image plane, image position, orientation, isocenter position and so on. Depending on image acquisition type the DICOM standard contains attributes for the modules both common to all image types as well as image specific attributes.
3 MATERIAL AND METHODS

3.1 TREATMENT PLANS

The Gamma Knife treatment plans used in the project were chosen and provided by an anonymous site. The clinical cases are relatively common cases, all real patients treated with the Gamma Knife and they are listed below. The cases are chosen due to the fact that they could show differences in contouring practice meaning experience, intuition, treatment modality and planning technique between Gamma Knife centers around the world. The number of observers participating in this study is 20. This resulted in 14 valid plans for anaplastic astrocytoma and AVM and 16 plans for vestibular schwannoma and meningioma. The participating centers in this study were given some instructions in the planning setup to make the analysis more robust. The instructions sent to the participating centers are given in APPENDIX 1. The most relevant instructions are target matrix size (to avoid interpolation) and center position of this. Otherwise they were told to perform the delineation and the planning following their own clinical routines.

3.1.1 ANAPLASTIC ASTROCYTOMA

A male patient, 45 years of age, was in 2004 surgically treated for lateral anaplastic astrocytoma. This was followed by 72 Gy of accelerated hyper-fractionated RT and chemotherapy with ACNU\(^6\). In 2009, recurrences were found and were treated in Gamma Knife with a 50% isodose of 16 Gy. Numerous images were available in the treatment planning process as shown in Figure 5. Pre-planning acquisitions are co-registered to the image sequences with the stereotactic frame attached.

3.1.2 MENINGIOMA

Female, 75 years of age found with a meningioma of the lateral cavernous sinus\(^7\) in the proximity to right optical nerve. The patient was presented with a dysfunction of III and IV cranial nerve causing double vision (diplopia) and a so called dropping eyelid (blepharoptosis). MRI, CT and a co-registration of these are available in treatment planning, as shown in Figure 6.

3.1.3 LATERAL VESTIBULAR SCHWANNOMA

Male, 61 years of age. The patient was presented with a neurological disorder called ataxia that affects coordination, balance and speech. Surgical resection was performed 3 months prior to Gamma Knife surgery and the patient suffered complete loss of hearing on the left ear. Examples of image studies available in the treatment planning are seen in Figure 7.

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\(^6\) Nimustine, chemotherapeutic agent.

\(^7\) A small blood filled space on either side of the base of the skull located behind the eyes. It contains critical arteries and nerves.
3.1.4 ARTERIOVENOUS MALFORMATION (AVM)

A male patient, 39 years of age found with lateral frontal AVM. Angiography and MRI were available for the treatment planning and the planner defined the target first with the help of angiography images. Lines are drawn from these images that define the target within a box conformal to the AVM. These lines are an important help when planning to the MRI images. Examples of image studies available in the treatment planning are seen in Figure 8.

![Image of MRI studies](image)

Figure 5. Anaplastic Astrocytoma. (a)MRI-FLAIR (b)PET (c) MRI-T2 (d) MRI-images
Figure 6. Meningiom. (a) MRI (b) CT-images.

Figure 7. Vestibular Schwannoma. (a) and (b) MRI (c) CT (d) MRI-images.
3.2 STRUCTURE AND VOLUME ANALYSIS

All received files are given in the lgp\(^8\)-format. These are supported by GammaPlan and the first step is to import data to the TPS and thereafter export them back from the treatment planning system as DICOM-files. In this step a resolution of 0.5 mm is chosen for the minimal resolution in upcoming calculations. It is feasible to export all data with a resolution finer than 0.5 mm but the export time was increased beyond reasonable limits. The exported data concerning the analysis includes target structures, DVH’s for skull and RT-Dose for target matrix. Analysis of treatment plans in LGP is

\(^8\) Lgp stands for Leksell Gamma Plan.
important for the identification of regions of interest (ROI’s) in the following structure analysis in MATLAB. This is the program chosen for the structure and volume calculations and gives a high-quality visualization of all structures. Image Processing Toolbox is one add on feature for MATLAB and contains valuable functions for performing the analysis. The script is written to be applicable to all RT-SS files and RT-Dose files with some modification to the separate clinical cases. Before exporting the data as DICOM files, all image sequences available for the planner were studied in order to locate one with the most slices of delineated structure. These were common to all observers and therefore no interpolation was needed in the inter-observer comparison.

After the first analysis in LGP is done, the target structure is identified in MATLAB and all contour data is identified to its image plane with the z-coordinate, a polygon is visualized in all slices to form a 3D plot, as shown in Figure 9.

Figure 9. 3D plot of delineated structures. (a) Anaplastic astrocytom (b) Meningioma (c) Vestibular schwannoma (d) AVM. The units on the axis are given in mm.
A feature in Image Processing Toolbox is the inpolygon function. This sets all values within the polygon of interest to one and all values outside to zero. The result of this is a binary image with an interpretation that values of one represent a part of delineated target and zero represent normal tissue surrounding target, as illustrated in Figure 10 where the structures are viewed in four slices of the image plane for each disorder. In this step the fine resolution of 0.5 mm of the DICOM export has a central role in defining the boundaries of target structure.

Figure 10. Binary structures in sliceplane view. (a) Anaplastic astrocytom (b) Meningioma (c) Vestibular schwannoma (d) AVM. The units on the axis are in mm.

A problem arising from the binary translation of images is that all polygons were correlated with one individual slice. Many of the plans have several polygons in the same slice and they had to be reinstalled to their actual slice. By knowing the image slice positions, which are repeated for multiple polygons in one slice, the correct structure can be identified. This step is computed in each individual script and thereafter automatically saved in the main script. All matrices are corrected.
before taken them into the script to be consistent with each other. In fact they are given the same size as the dose matrices to be compatible in the radiobiological analysis. The process of doing this in a way which does not demand manual inputs is not trivial and requires the x,y and z start positions of all plans. They are retrieved from the information regarding dose-matrices. Here the DICOM tag “Image Position Patient” gives 3D start coordinates of the target matrix set by the planner. The information regarding the size of the target matrix was obtained from the original plans. Problems aroused due to the fact that not all planners agreed on the size of the target matrix. In some cases the matrix was increased in size to cover all delineated volume or decreased to access higher dose calculation accuracy. The worse scenario is when the target matrix center point was altered also. This was allowed in the planning process agreement but required some interpolation to be in consistency with all plans. In the general instructions to the planners it was important not to affect the observers view on the planning process too extensively. Set up instructions were therefore formulated more as a guideline for an easier comparison. The observers were able to make the changes needed as long as they gave some input to their reasons. Most of the observers followed the instructions and the study was therefore not highly affected by interpolation between values.

10 of the plans included in this study were constructed with the direct settings of shots without the delineation of target. The reason for this is both treatment strategy of planner and Gamma Knife site and the inability of delineating target structure. Volume calculation in these cases is based on the dose matrix. The matrix is first interpolated to an interslice distance the same as the one of the structure matrix, the initial distance is given from the DICOM export of 0.5 mm. All values higher or the same as the prescribed dose to 50% or any other prescribed isodose surface that may have been applied are set to unity and all the other values to zero. Thus a similar binary matrix is constructed and the analysis is followed as with the structure based binary matrices. Figure 11 shows an example of an isosurface image of the prescribed isodose for all four disorders. This is the corresponding structure image to the series of polygons showed in Figure 9 when no target structure is delineated. All values within these surfaces correspond to the prescribed isodose or higher. The lack of structure delineated leads to the impossibility to determine the conformity of the plan. However, it is possible to measure the dose fall-off and include these cases in the inter-comparison of volumes between plans. The planning methods differ conceptually but the aimed treatment endpoint is the same.
3.2.1 VOLUME CALCULATION

Volume calculation was performed in a similar manner as done in the LGP by approximating the volume between two slices as the volume calculated by adding the ones of two sequent slice areas multiplied by half of the interslice distance and doing this as a loop covering all slices. This method is refined by adding the volumes of one voxel outside the first and last slice. The calculated volumes are comparable with the volumes from LGP. The reason for not using directly the volumes from the LGP was to avoid errors from the plans where several structures were delineated for one target. The union of these structures calculated in MATLAB is in fact the true target for the plan in concern and the calculated volume is more reliable than the added volume from LGP.
3.2.2 AVERAGE TARGET

The targets delineated by the observers participating in this study were combined for determining the average target or “true target”. This should define the region with the highest probability of target structure based on some key assumptions. In the present study the average target is based on the assumption that all observers performed the planning within the same frame regarding e.g. image sequences, patient information and study instructions. Calculation of average target is done with the assumption that this is the volume delineated by half of the observers. In other words it is simply done by adding all binary target structures and the result is a structure with a central part of value the same as the number of observers included in the study, as illustrated in Figures 12-15 where the added matrices are displayed in one slice. Values outside the maximum central part are slowly decreasing to zero with the half maximum value approximated as average volume boundary. Voxels included in the target by half the number of observers are set to one and the remaining to zero. In this way the volume of average target is calculated by knowing pixel size and interslice distance and the calculation is performed the same way as the for the volume of each individual observed structure. The interslice volume is weighted by each slice area. This volume represents the average volume of target if the assumption is made that all observers delineate with the same clinical demands. In this study this target is assumed to be the true pathology to be treated for each disorder.

Figure 12. Anaplastic astrocytoma added matrix in one slice view. The grey scale shows the number of observers. White corresponds to complete or highest level of agreement. The units on the axis are in mm.
Figure 13. Meningioma added matrix in one slice view. The grey scale shows the number of observers. White corresponds to complete or highest level of agreement. The units on the axis are in mm.

Figure 14. Vestibular schwannoma added matrix in one slice view. The grey scale shows number of observers. White corresponds to complete or highest level of agreement. The units on the axis are in mm.

Figure 15. AVM added matrix in one slice view. The grey scale shows number of observers. White corresponds to complete or highest level of agreement. The units on the axis are in mm.
3.2.3 COMMON AND ENCOMPASSING VOLUME

The central part of the target common to all observers, i.e. common volume (Rasch et al. 1997), is compared to average volume. An ideal case is when this volume is the same as the average volume which in turn is the same as all individual volumes. The calculation of the common volume is based on the added matrix and values of unity which are distributed to all voxels delineated by all the observers.

Encompassing volume (Rasch et al. 1997) is the union of the volumes delineated by all observers and represents all nonzero values with the bounding contour at the border of volume delineated by all observers; comparison with the average target volume is made. The ideal case is the same as mentioned above and a high inequality with common volume is an indication of large differences in target sizes and positions for all individual observers. Figure 16 illustrates the common and the encompassing volume.

![Figure 16](image)

Figure 16. A: Encompassing volume, B: Common volume.

3.2.4 CONCORDANCE AND DISCORDANCE INDEX

Concordance index (CCI) is calculated as the ratio of common volume and the encompassing volume for the average target volume and the individually delineated target volumes, \( \frac{(V_1 \cap V_2)}{(V_1 \cup V_2)} \). The ideal case is when there is no displacement of the two volumes and they are of the same size and shape (CCI=1). The Discordance Index (DCI) is calculated as the volume of average target which is not covered by each individual observed target volume, \( V_1 - (V_1 \cap V_2) \). When the average target is completely covered by the individually delineated volume the discordance index is zero. On the assumption made in this study, that the average target should resemble a true target, any result of the DCI higher than zero is the indication of an over- or under-treatment or both.
3.2.5 CONFORMITY INDEX
In 1993, the Radiation Therapy Oncology Group (RTOG) proposed several parameters for the evaluation of stereotactic RT treatment plans. One of these parameters is the conformity index (CI) which is the ratio between the volume of target contained within the reference isodose volume and target volume $V_{TP}/V_T$ (Shaw et al. 1993, Yomo et al. 2010). A CI of one represents an ideal case of perfect conformity while an index lower than one corresponds to under-treatment. A value below one indicates lower target coverage but does not give any information on the volume of normal tissues irradiated. The conformity index is in clinical terms known as the coverage.

3.2.6 PADDICK CONFORMITY INDEX
Another measure of how well a radiosurgical treatment plan conforms to the delineated target volume is the Paddick Conformity Index (PCI) and is defined as $(V_{TP}/V_T) \times (V_{TP}/V_p)$ where $V_{TP}$ is the volume of target contained within the prescription isodose surface, $V_T$ is total target volume and $V_p$ is the prescription isodose volume (Paddick 2000). This yields a score of unity for a perfectly conformal plan and do not produce false perfect scores. The less conformity a plan has, the lower the PCI is and both over-treatment and under-treatment is regarded as equally worsening the conformity. Over-treatment ratio is $1 - V_{TP}/V_p$ and under-treatment is $1 - V_{TP}/V_T$. For example, a conformity index of 50% or 0.5 translates into 50% conformity between prescribed isodose and delineated structure. This value of the PCI indicates either over-treatment (prescribed isodose surface volume larger than target volume) or under-treatment (prescribed isodose surface volume smaller than target volume).

3.2.7 GRADIENT INDEX
Gradient index (GI) gives the measure of dose fall-off outside prescribed isodose volume. It is simply calculated by the ratio of prescribed isodose volume and the volume of half prescribed isodose volume (Paddick and Lippitz 2006). In this study these are 50% isodose volume and 25% isodose volume. Figure 17 shows the 50% isodose and the 25% isodose in LGP for all 4 disorders. The corresponding volumes are retrieved from the dose matrices converted into binary matrices; the volumes are calculated in the same manner as previously described. Volumes receiving 50% and 25% of maximal dose can as well be found in LGP and a comparison with the result of GI based on these is made with binary calculations. This should yield values comparable to each other. When studying the dose distribution inside the target matrix in LGP it is noticeable that the 25 % isodose volume is distributed somewhat outside the target matrix in practically all plans. One perfect value of 1 is never achieved. Instead, a gradient index less than 3 is regarded as high. To spare critical
structures and normal tissue surrounding target, the dose fall-off should always be optimized with a balance to the treatment plan optimization.

All parameters for target volume comparison are summarized in Table 1.

Figure 17. 50% and 25% isodose lines. (a) Anaplastic astrocytom (b) AVM (c) Meningiom (d) Vestibular Schwannoma.
Table 1. Evaluation parameters for comparison of rival plans.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Expression</th>
<th>Ideal Case</th>
<th>Clinically acceptable values</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concordance Index</td>
<td>(\frac{(V_1 \cap V_2)}{(V_1 \cup V_2)})</td>
<td>1</td>
<td>-</td>
<td>Ratio of common volume and encompassing volume, (V_1=)average volume, (V_2=)observed volume</td>
</tr>
<tr>
<td>Discordance Index</td>
<td>(V_1 - (V_1 \cap V_2))</td>
<td>0</td>
<td>-</td>
<td>Amount of average volume ((V_1)) not covered by observed volume ((V_2))</td>
</tr>
<tr>
<td>Conformity Index</td>
<td>(\frac{V_{TP}}{V_T})</td>
<td>1</td>
<td>-</td>
<td>(V_{TP}=)Volume of target contained within prescription isodose volume, (V_T=)target volume</td>
</tr>
<tr>
<td>Gradient Index</td>
<td>(\frac{V_{25%}}{V_{50%}})</td>
<td>1</td>
<td>1-3</td>
<td>Measure of dose fall-off outside prescribed isodose volume=(V_{50%})</td>
</tr>
<tr>
<td>Paddick Conformity Index</td>
<td>(\frac{(V_{TP}/V_T)^*(V_{TP}/V_p)})</td>
<td>1</td>
<td>-</td>
<td>(V_p=)Prescribed isodose volume Measure of both under-treatment and over-treatment</td>
</tr>
</tbody>
</table>
3.3 RADIOBIOLOGICAL ANALYSIS

The inter-observer variability in delineating the target and the influence on the treatment outcome were evaluated from the radiobiological point of view by assessing the tumor control probability for meningioma, astrocytoma and vestibular schwannoma and the probability of obliteration for AVM. The resulting differences in the irradiation of the normal brain outside the target due to variability in delineating the target were also evaluated with respect to the risk of secondary cancer.

3.3.1 TUMOR CONTROL PROBABILITY

Tumor response described in terms of tumor control probability (TCP) could be calculated using Poisson statistics based on the initial number of clonogenic cells and the cell survival after a dose $D$ given in one fraction as:

$$TCP = \exp\left(-\sum_{i=1}^{n} \rho_0(V_i) V_i e^{-\alpha D_i - \beta D_i^2}\right)$$

where $N_0$ is the initial number of clonogenic cells in the tumor and cell survival is described by the LQ model assuming that the distribution of the cells within the tumor is homogeneous and the cells have the same sensitivity to radiation and receive the same dose, $D$. For voxel-based calculations in case of non-homogeneous distribution of the dose, Equation 3 above transforms into a summation over the tumor voxels with volumes $V_i$ as:

$$TCP = \exp\left(-\sum_{i=1}^{n} \rho_0(V_i) V_i e^{-\alpha D_i - \beta D_i^2}\right)$$

where $n$ is the total number of voxels, $\rho_0(V_i)$ is the initial density of clonogenic cells in voxel $i$, $V_i$ is the volume of voxel $i$, and $D_i$ is the dose received by the cells in voxel $i$.

The general expressions above could be used for response calculation irrespective of the size or shape of the tumors under the assumptions of even intrinsic radiation sensitivity of the cells as long as the dose to the voxel is known. In order to determine the dose in each voxel in the structure matrix, dose matrices which are exported with a resolution of 0.5 mm were interpolated in the z-direction in order to match the resolution of the structure matrices which have an interslice distance given by the distance of imaging method imported in the LGP. All structure matrices were redefined to have the same number of slices as the dose matrices.

A few assumptions regarding the number and the distribution of clonogenic cells were made based on the specific pathology of meningioma, astrocytoma and vestibular schwannoma,
respectively. The average calculated target was assumed to be the “real” target for all brain disorders. The total amount of clonogenic cells in the average target was calculated based on the slope $\gamma$ of clinical dose-response curves for each of the pathologies as $N_0 = \exp(\gamma e)$. The density of cells in each voxel is then calculated by the known number of voxels and voxel-size inside each target. For each case under analysis an “infiltrative power” was defined in order to account for the fact that some of the tumor cells might infiltrate into the normal tissue outside the average target following a pattern depending on the specific pathology of the investigated brain disorder. Each infiltrative power was thus defined by a density function. The relative value of this function is decreasing with distance from structure border. The nearest distance to the structure was thus calculated in every voxel outside the structure border and a matrix of these values was defined. The clonogenic cell density in each voxel inside the structure was kept constant while the density outside structure border was calculated based on the distance to structure border and the density function. The infiltration power is based on an estimation of the maximal distance at which clonogenic cells could be found outside the well delineated target. For astrocytoma the maximal distance for infiltration was based on a study by Yamahara et al. (2010) on the comparison between examined autopsy brains and MR images for glioblastoma in which it was found a peripheral tumor boundary infiltration of 6-14 mm. Glioblastoma is a highly infiltrative glioma the same as astrocytoma. This sets the limit of infiltration of all cases with the astrocytoma as the highest infiltrating lesion. The assumed functions describing density of clonogenic cells outside delineated target and the maximal distances of infiltration clinically relevant for the pathology of interest are given in Table 2 and plotted in Figure 18. In Figure 19 the average target is displayed together with maximal distance of infiltration for meningioma, astrocytoma and vestibular schwannoma. This figure illustrates as well the relative density of infiltration in one slice where a value of 1 gives the cell-density inside the target.
Table 2. Functions describing density of clonogenic cells outside the delineated target.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Function of infiltration density</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Astrocytom</td>
</tr>
<tr>
<td>$f(r)$</td>
<td>$f(r) = e^{-r/3}$</td>
</tr>
<tr>
<td>Maximal distance of infiltration [mm]</td>
<td>12</td>
</tr>
</tbody>
</table>

Figure 18. Functions of infiltration.
Figure 19. Illustration of infiltration for astrocytoma (top), meningioma (middle) and vestibular schwannoma (bottom). Left images shows the relative infiltration density in one slice and right images shows the average target with the maximum distance of infiltration for all three disorders. The units on the axis are given in mm.

The values of the parameters used in the calculation of the TCP for meningioma, astrocytoma and vestibular schwannoma are given in Table 3. The $\alpha/\beta$-ratio used for meningioma and vestibular schwannoma were calculated as the average values of the intrinsic radiation sensitivity to
fractionation reported in the study by Vernimmen and Slabbert (2010) and Shrieve et al. (2004). Individual $\alpha$ and $\beta$ values for meningioma and vestibular schwannoma were calculated based on their specific $\alpha/\beta$-ratio assuming that the surviving fraction of cells after 2 Gy is 50%. The $\alpha/\beta$-ratio as well as the individual $\alpha$ and $\beta$ parameters for astrocytoma were assumed to be the same as for glioblastoma reported by Malaise et al. (1986).

The $\gamma$-value for these three brain disorders was approximated based on the relative slope of the dose-response curves knowing that astrocytoma is the disorder with the steeper slope and meningioma and vestibular schwannoma are characterized by shallower curves.

Table 3. Radiobiological parameters used in the calculation of the TCP for astrocytoma, meningioma and vestibular schwannoma.

<table>
<thead>
<tr>
<th>Brain disorder</th>
<th>Astrocytoma</th>
<th>Meningioma</th>
<th>Vestibular Schwannoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha/\beta$ (Gy)</td>
<td>8.31</td>
<td>3.45</td>
<td>2.09</td>
</tr>
<tr>
<td>$\alpha$ (Gy$^{-1}$)</td>
<td>0.24</td>
<td>0.22</td>
<td>0.18</td>
</tr>
<tr>
<td>$\beta$ (Gy$^{-2}$)</td>
<td>0.03</td>
<td>0.06</td>
<td>0.08</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>5</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

3.3.2 AVM OBLITERATION PROBABILITY

Treatment endpoint for AVM is different than those for the other brain disorders subject of investigation in this thesis. Endpoint in treating AVM is complete obliteration of the malformation. The model for obliteration and the corresponding parameters were taken from a study by Mavriodis et al. (2002). The proposed model for the probability of causing AVM obliteration is the linear Poisson model described by Equation 5, where $D_{50}$ is the dose which gives a response of 50% and $\gamma$
is the dose response gradient. These two parameters characterize the shape of the dose-response relation for AVM obliteration. This expression assumes that the nidus is irradiated uniformly with a dose $D$. For heterogeneous dose distributions the response of the AVM using the linear Poisson model is then given by Equation 6. The values of $D_{50}$ and $\gamma$ are calculated for a reference volume of $3 \text{ cm}^3$ and $\Delta v_i = \Delta V_i / V_{\text{ref}}$ is the fractional irradiated subvolume of the AVM receiving dose $D_i$ relative to the reference volume. $M$ is the total number of voxels or subvolumes in the AVM receiving dose $D_i$.

$$P(D) = \exp(-e^{-\gamma - \left(\frac{D}{D_{50}}\right)(\gamma - \ln 2)})$$  \hspace{1cm} (5)$$

$$P(D) = \prod_{i=1}^{M} [P(D_i)]^{\Delta v_i}$$  \hspace{1cm} (6)$$

Probability of AVM obliteration is calculated with the same basic idea as for the TCP. It is done voxel by voxel and truncation errors are avoided by summing the logarithmic value of the probability for each voxel. The parameters used in the calculations are taken from Mavriodis et al. (2002) and they are shown in Table 4.

<table>
<thead>
<tr>
<th>Brain disorder</th>
<th>AVM</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_{50}$ (Gy)</td>
<td>22.9</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>1.25</td>
</tr>
</tbody>
</table>

### 3.3.3 RISK OF SECONDARY CANCER

The competition model for evaluating the risk of secondary cancer is a non-linear model which takes into account the competition between cell survival and induction of carcinogenic mutations as described by Equation 7 (Dasu et al. 2005).
\[ Effect(D_i) = (\alpha_1 D_i + \beta_1 D_i^2) \cdot e^{-\left(\alpha_2 D_i + \beta_2 D_i^2\right)} \]  

(7)

In order to account for the inhomogeneous dose distribution received by the normal brain outside the target the complete dose distribution was used and calculations were made for each dose interval of the DVH and then they were weighted by volume as described by Equation 8.

\[ Total\ effect = \frac{\sum_i (v_i \cdot Effect(D_i))}{\sum_i v_i} \]  

(8)

where \(v_i\) is the volume of tissue receiving dose \(D_i\) and \(Effect(D_i)\) is the nonlinear dose response relationship of the competition model given by Equation 7.

Values of the parameters used in the model are given in Table 5. The \(\alpha/\beta\) value for normal brain was assumed to be 2 Gy. For \(\alpha_1\) parameter the reference is ICRP60 (ICRP Publication 60) corresponding to half of the risk for the "remainder" multiplied by 2 to account for the high dose rates used in radiotherapy. For \(\alpha_2\) the reference is Dasu et al. (2005) in which the assumptions for the numerical value were based on an epidemiological study by Dörr and Hermann (2002).

Table 5. Radiobiological parameters used in the calculation of the risk of secondary cancer in the brain.

<table>
<thead>
<tr>
<th>(\alpha/\beta) (Gy)</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha_1) (Gy(^{-1}))</td>
<td>0.010</td>
</tr>
<tr>
<td>(\beta_1) (Gy(^2))</td>
<td>0.005</td>
</tr>
<tr>
<td>(\alpha_2) (Gy(^{-1}))</td>
<td>0.250</td>
</tr>
<tr>
<td>(\beta_2) (Gy(^2))</td>
<td>0.125</td>
</tr>
</tbody>
</table>
4 RESULTS AND DISCUSSIONS

4.2 STRUCTURE AND VOLUME ANALYSIS

Average target volume was defined as the volume of the constructed structures based on the binary 3D matrix common for 50% of the observers. This is compared to the mean volume and the median volume of all delineated target volumes. The mean volume is thus not the same as the average volume. Taking into account the complexity and shape of the target large differences between mean target and average target volume were detained. The mean volume is therefore the average of all volumes calculated in MATLAB. This value is given together with the standard deviation of the mean as a measure of the spread of values in the distribution of volumes. The median volume shows how the distribution of delineated volumes is shifted. The differences between calculated volume and volume given in LGP are not experimentally presented in this report. However, the differences in the calculated volumes compared to LGP were found larger for the smaller delineated volumes. In these cases the addition of one voxel at the first and last slice heavily compensated for the differences. For the larger volumes these additions were not resulting in a volume in better concordance with the LGP in all cases. Average target volumes for all four cases are given in Table 6 together with mean volume, median volume, maximum volume and minimum volume. Encompassing volume and common volume are also given in Table 6. The minimum and maximum deviations from the LGP are also given as a measure of the robustness of the volume calculation method used in this study.

In Figures 20-23 the average target volume, encompassing and common volumes are displayed as isosurface plots in order to illustrate the differences between those volumes.
Table 6. Volume analysis for all four brain disorders.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Astrocytom</th>
<th>Meningioma</th>
<th>Vestibular Schwannoma</th>
<th>AVM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average Volume</strong></td>
<td>2.06</td>
<td>5.90</td>
<td>4.91</td>
<td>11.86</td>
</tr>
<tr>
<td>[cm$^3$]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean Volume</strong></td>
<td>5.90±6.21</td>
<td>6.53±0.74</td>
<td>5.98±2.11</td>
<td>12.78±4.83</td>
</tr>
<tr>
<td>[cm$^3$]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median Volume</strong></td>
<td>2.88</td>
<td>6.67</td>
<td>6.40</td>
<td>12.55</td>
</tr>
<tr>
<td>[cm$^3$]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Min Volume</strong></td>
<td>1.66</td>
<td>4.96</td>
<td>0.44</td>
<td>3.48</td>
</tr>
<tr>
<td>[cm$^3$]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Max Volume</strong></td>
<td>21.45</td>
<td>7.69</td>
<td>8.78</td>
<td>21.05</td>
</tr>
<tr>
<td>[cm$^3$]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Max deviation from LGP</strong></td>
<td>2.05</td>
<td>0.12</td>
<td>0.15</td>
<td>3.28</td>
</tr>
<tr>
<td>[cm$^3$]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Min deviation from LGP</strong></td>
<td>5.50×10$^{-3}$</td>
<td>0.63×10$^{-3}$</td>
<td>1.25×10$^{-3}$</td>
<td>0.02</td>
</tr>
<tr>
<td>[cm$^3$]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Common Volume</strong></td>
<td>0.05</td>
<td>2.60</td>
<td>0.31×10$^{-3}$</td>
<td>1.36</td>
</tr>
<tr>
<td>[cm$^3$]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Encompassing Volume</strong></td>
<td>43.27</td>
<td>13.14</td>
<td>15.80</td>
<td>27.27</td>
</tr>
<tr>
<td>[cm$^3$]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.2.1 VOLUME COMPARISON FOR ANAPLASTIC ASTROCYTOMA

Larger difference between common volume and encompassing volume was found for anaplastic astrocytoma due to differences in treatment approach, volume delineated, images used in the planning process. A large difference between these two volumes is a clear evidence of a higher complexity in the planning process.

In the volume comparisons for astrocytoma large discrepancies in the delineated target volume could be observed. Between the largest and the smallest volume there is a difference of 20 cm$^3$. There are not outliers among the delineated volumes with respect to the location in this analysis; instead the volumes are rather evenly distributed within the encompassing volume. Regarding the size of the volumes, there are more values within the lower range of volumes as indicated also by the median value. This large disagreement between observers in delineating the target resulted in an average target with a relatively small volume in comparison to the mean volume. The common volume is extremely small in comparison to the encompassing volume, as illustrated in Figure 20 b and shown in Table 6. This is due to the multi focal appearance of this lesion and due to the fact that several imaging modalities were available for delineation. The PET sequence was of free choice for the observer to take into account for the target delineation. In order to receive plans that resembled the clinical reality as much as possible. The observers were instructed to choose freely from the imaging sequences with the input that they should have them available at their site. The inputs from the observers, given in APPENDIX 2, clearly stated how they planned in particular for the astrocytoma. The result is thereafter, the fact that the delineated volume is dependent on the observers’ access to PET imaging. The average target volume is 3.84 cm$^3$ smaller than the mean volume and 0.82 cm$^3$ smaller than the median volume. Reasons for the fact that the average target volume is that small compared to the mean volume are due to the large differences in the treatment plans received. This is also illustrated in Figure 20 a. The differences in target volume, placement of target structure, choice of imaging modality all have a large impact on the result. The standard deviation of the mean is larger than the value itself and indicates that the volumes included are far from the mean which could also be seen by looking at in the maximum value and minimum value of the data. The largest deviation in the volume calculation is observed when there are several structures drawn for the same target and the complete volume in LGP is therefore the summation of these which gives an overestimation of the true volume.
Figure 20. Anaplastic astrocytoma: (a) Average volume (blue) versus encompassing volume (red), (b) Common volume (blue) versus encompassing volume (red). Representation of units on the axis is expressed in mm.

4.2.2 VOLUME COMPARISON FOR MENINGIOMA

Regarding the target delineations of meningioma and the resulting volumes, the average volume is only slightly smaller than both the mean and median volume as shown in Table 6. The interpretation of this is that although the volumes are of the approximate same size, the target structures differ in position. The mean and median volume differs by only 0.14 cm³. A small trend towards larger volumes was noted. The difference between the common volume and encompassing volume is 10.55 cm³ and this is the evidence of target volume discrepancies in position and shape, as shown in Figure 21 b. This difference is even larger than the largest structure delineated and there are several reasons for this such as the choice by planner of which images to employ in the planning process among the several diagnostic images available, clinicians apprehension of target structure and the planning practice of the sites involved. Despite the somewhat large differences in the position of target, the absolute values of volumes to be treated do not differ to the same amount. In APPENDIX 2 the reflections of planners involved show that they focused largely on the sparing of critical structures, the optic apparatus. If the planner sets a high weight on the sparing of OAR the target delineation could have been translated towards the more distal end with respect to the critical structures. On the other hand, another planner may still have delineated the target with the pathology at hand and thereafter placed all shots and blockings to encompass a dose to OAR below critical value. Both approaches are valid. The measures of target structure coverage could be
indications of which method is applied. The average target is positioned fairly central of the encompassing volume structure; the distribution of volumes delineated for treatment is therefore evenly placed around the average target, as shown in Figure 21 a. The image modalities available for the treatment setup for this case were limited in comparison with astrocytoma and vestibular schwannoma which limits the choices for the observers and the variation in target shape, size and position could be affected by this.

Figure 21. Meningioma: (a) Average volume (blue) versus encompassing volume (red), (b) Common Volume (blue) versus encompassing volume (red). Representation of units on the axis is expressed in mm.

4.2.3 VOLUME COMPARISON FOR VESTIBULAR SCHWANNOMA

In Table 6 the volume measures are reported for vestibular schwannoma. Figure 22 shows the encompassing volume compared to the average volume and the common volume is displayed together with the encompassing volume. The common volume is difficult to visualize inside the encompassing volume due to the fact that it has the size of one voxel. Thereby, there was almost no part of the lesion that all observers agreed on in the treatment planning and target delineation. The average volume is smaller than both the mean volume and the median volume. This is due to the amount of differences in target apprehension. Since the lesion involved is the recurrence of a previous surgically treated target and scattered around the surgical resection, large discrepancies are present in location. The differences in target volumes solely are not higher than would be expected. Average target volume is 1.07 cm³ smaller than the mean volume and the median volume is 0.42 cm² larger than the mean volume. The difference between the largest and the smallest delineated
volume is 8.29 cm³. In the process of treatment planning, there are several diagnostic images available. The complete treatment plan is therefore highly dependent on the choice of image for delineation. It is clear from the view on the individual plans that some observers delineate with the use of several images at hand and other only look at one single sequence of images. This is the appearance of some of the plans. Another large contribution to the delineation of the target is whether the observer accounted for the deafness of the patient or not. Since the patient had lost completely the hearing on the ear close to the target, the dose received by the cochlear apparatus is not of concern. When studying the received plans, the cochlea was delineated as a critical structure in some cases and this is not something that is critical for the treatment. Some reflections from observers stated that the evaluations of the contrast enhanced structures are difficult to perform. The short time-span between surgery and LGK treatment might indicate that some of the contrast enhanced structures have occurred due to vascular changes in the tissues surrounding the lesion. The result of this is a highly complex plan with a less optimal dose fall-off and a target matrix size very large to cover the entire lesion. Smaller matrices result in more accurate dose calculations and several matrices are required for complete cover. These matrices could overlap each other and the analysis of this is complicated. The deviations in the volumes are as well seen in Table 6. The max deviation comes from one plan based on several structures delineated. The complete volume is simple the addition of these and results in an overestimation of the volume. The calculated volume in MATLAB is therefore more accurate.

Figure 22. Vestibular Schwannoma: (a) Average volume (blue) versus encompassing volume (red), (b) common volume (blue) versus encompassing volume (red). Representation of units on the axis is expressed in mm.
4.2.4 VOLUME COMPARISON FOR AVM

The volumes determined for AVM are shown in Table 6. The mean and median values of volumes are similar which indicates that the volumes are evenly distributed around the mean value. It does not say how wide this distribution is. This is instead given by the standard deviation of 4.83 cm$^3$ which indicates a rather large distribution of volumes around the mean value. This could also be indicated by the range between the min volume and the max volume which is 17.57 cm$^3$. Many observers reported that the angiography images were not optimal for the indication and that it was difficult to completely distinguish the AVM nidus. This may contribute to an over- or underestimation of the true target. The max deviation in the calculated volumes compared to the treatment planning system is because the volume in LGP is the summation of several volumes. The observers had numerous images available for delineation when performing the treatment plan and this could be another reason for the differences in the volumes together with variations in treatment experience and the observers’ input to the validity of the case for LGK. The average target volume indicates that the majority of observers delineated a structure centered in approximately the same area but the difference is in the size of the structure, as shown in Figure 23 a. It is approximately of the same size as the median and mean volume. Despite this agreement of position there is a large difference between common volume and encompassing volume of 25.91 cm$^3$, as shown in Figure 23 b.

Figure 23. AVM: (a) Average volume (blue) versus encompassing volume (red), common volume (blue) versus encompassing volume (red). Representation of units on the axis is expressed in mm.
Results on the volume comparisons and measures for plan conformity and comparisons with average target are given in Tables 7-10. Concordance index and discordance index are measures which compares each observed volume with the average volume in size, position and shape. Conformity index, Paddick conformity index and gradient index compare each observed volume with their corresponding dose-distribution.

4.2.5 PLAN CONFORMITY FOR ANAPLASTIC ASTROCYTOMA
The parameters describing the plan conformity for astrocytoma are given in Table 7 and Figures 24-28. It could be seen that the optimal value of CCI is not achieved in any of the plans for meningioma as illustrated in Figure 24. For the first two indexes the individual structures are compared to the average target. As shown in Table 6, the average target is smaller than the other volumes. Two structures delineated by the observers resulted in a value of zero or approximately zero for CCI. This is due to the fact that the common volume of these two structures with the average target structure (intersection) is close or equal to zero. These large discrepancies are due to the complexity of the astrocytoma and that there is not one optimal choice of plan. Three delineated structures resulted in a value higher than 0.7 that indicates that those structures are similar to the average target. The DCI shows how much of the average target is missed in each individual plan. The fraction of average target not included in each delineated volume is calculated and shown in Figure 25. All values except the two extremes that are mentioned above for CCI resulted in a corresponding index of well below 50% of the DCI. If the average target is to be regarded as a valid measure for the true target, the differences between the average target and the observed target could be clinically significant. The amount of delineated target volume not covered by the prescribed isodose is given by the CI and illustrated in Figure 26. For one observer the resulting CI is 0.77 which could be significant if the observer aimed for target coverage while planning. This is the value coupled with the lowest score of the PCI. The PCI was not calculated for four of the observers because either the analysis was based on the dose matrix or several structures were delineated for one target. The ideal value of the PCI is 1 and that would indicate that the prescribed isodose perfectly conforms to the delineated structure. Several plans result in a relatively high PCI of 0.70 or well above which is shown in Figure 27. The remaining plans have a lower index and this is explained as previously by the complexity of the case. For the GI the uncertainty is due to the fact that that some of the 25% isodose volume may lie outside the target matrix which the analysis is based on. More than half of the plans have a GI higher than 3. The remaining plans can be considered as approved regarding the dose fall-off purely. The GI is illustrated in Figure 28. When studying some of the received plans for this case it is clear that the observer sometimes guide the 25% isodose line towards an area of suspicious target structure. This means that the dose fall-off is
not maximized surrounding the structure but instead optimized covering all the target areas of lower contrast enhancement. The GI is therefore not an optimal index for scoring the plans made with this method. One has to study the plans individually to distinguish these and have insight into the pathology of the brain disorder to be able to use the GI as a measure of plan quality.

Table 7. Plan conformity indexes for astrocytom.

<table>
<thead>
<tr>
<th></th>
<th>Concordance Index (CCI)</th>
<th>Discordance Index (DCI) [cm³, %]</th>
<th>Conformity Index (CI)</th>
<th>Paddick Conformity Index (PCI)</th>
<th>Gradient Index (GI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td>0.45</td>
<td>0.58</td>
<td>0.91</td>
<td>0.69</td>
<td>3.41</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>0.49</td>
<td>0.50</td>
<td>0.93</td>
<td>0.73</td>
<td>3.12</td>
</tr>
<tr>
<td><strong>Max</strong></td>
<td>0.85</td>
<td>2.06</td>
<td>0.96</td>
<td>0.83</td>
<td>6.82</td>
</tr>
<tr>
<td><strong>Min</strong></td>
<td>0</td>
<td>0</td>
<td>0.77</td>
<td>0.42</td>
<td>2.76</td>
</tr>
</tbody>
</table>

4.2.6 PLAN CONFORMITY FOR MENINGIOMA

The parameters describing the plan conformity for meningoma are seen in Table 8 and Figures 24-28. The CCI is the measure of how much of the average target is covered by each individual planned structure. A value higher than 0.5 implies that the volume of average target included in the planned volume is higher than the volume of normal tissue within the target, assuming that the average target is the true target. The result for meningioma shows that all of the observed structures result in a CCI higher than 0.5 and that the mean and median values are as well higher than 0.5, as well illustrated in Figure 24. However it is not possible to determine the clinical significance in the value of CCI. Higher values of the index are the result of a better concordance between the
delineated structure and average target, in shape, size and position. In Figure 25 it is shown that the DCI values display the highest consistency of all disorders evaluated. The CI values for meningioma indicate that a small amount of delineated target is not covered by the prescribed isodose. The value of PCI for one observer is not given since the structure analysis is based on dose and there is no structure delineated in this plan. One plan has the value of 0.53 for PCI; otherwise all plans result in an index of 0.7 or above. The GI is regarded as clinically acceptable if it is between 1 and 3. All plans resulted in an accepted dose fall-off except one. With the full dose distribution surrounding the structure, a more accurate gradient index could be calculated for all plans.

Table 8. Plan conformity indexes for meningioma.

<table>
<thead>
<tr>
<th></th>
<th>Meningioma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conformity Index (CCI)</td>
</tr>
<tr>
<td>Mean</td>
<td>0.71</td>
</tr>
<tr>
<td>Median</td>
<td>0.72</td>
</tr>
<tr>
<td>Max</td>
<td>0.87</td>
</tr>
<tr>
<td>Min</td>
<td>0.50</td>
</tr>
</tbody>
</table>

4.2.7 PLAN CONFORMITY FOR VESTIBULAR SCHWANNOMA
The CCI and DCI for vestibular schwannoma are shown in Table 9 and Figures 24-28. The values for the majority of plans for the CCI are between 0.40 and 0.70 as shown in Figure 24. This indicates either that the intersect between the average target and observed target is small or that the
intersect may be covering almost the entire average target but the observed target is much larger. The complexity of this case is derived from the fact that it is previously surgically treated and the remaining target are scattered around this resection. There is a large disagreement on which areas of contrast enhancement are in fact showing tumor cells and which that are vascular deformations due to the surgery. The lowest value of the CCI corresponds to the smallest delineated volume. Although it may be covered by the complete average target structure, the average target volume is much larger. A more realistic scenario is that it is partly included in the average target structure. The lowest value of the CCI corresponds to the highest value of the DCI. The majority of the plans have delineated structures that give a DCI below 30% of the average target and about half of the plans have a value below 20% as illustrated in Figure 25. If the average target is to be regarded as the real target, the areas not included in each delineated volume are of high concern for the treatment result and could be clinically significant. When analyzing the values of the CI one could observe one low value, the rest indicating a high conformity between the prescribed isodose and the delineated target as shown in Figure 26. The PCI was not calculated for two observers where no structure was delineated. Many of the observers have delineated a highly asymmetrical target and it is therefore difficult to keep the PCI high when the prescribed isodose volume does not conform to the delineated structure. The index does not indicate whether the plan is acceptable or not, the observer might have delineated a perfect structure and planned from the perspective of covering the entire lesion. Treatment outcome may still be satisfying despite a somewhat low index. In this study, the documentation of this measure has more the purpose of comparing the observers’ methods of planning on a delineated structure. The same observation is made for this case as for the astrocytoma; a few observers have covered the most speculative areas with the 50% isodose lines and the suspicious areas with the 25% isodose lines. This yields a larger 25% volume of the prescribed dose and the GI is not a fair measure of the treatment plan quality. The PCI is illustrated in Figure 27 and the GI in Figure 28.
### Table 9. Plan conformity indexes for vestibular schwannoma.

<table>
<thead>
<tr>
<th></th>
<th>Concordance Index (CCI)</th>
<th>Discordance Index (DCI) [cm³, %]</th>
<th>Conformity Index (CI)</th>
<th>Paddick Conformity Index (PCI)</th>
<th>Gradient Index (GI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td>0.53</td>
<td>1.13</td>
<td>0.96</td>
<td>0.69</td>
<td>3.21</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>0.54</td>
<td>0.74</td>
<td>0.97</td>
<td>0.70</td>
<td>3.16</td>
</tr>
<tr>
<td><strong>Max</strong></td>
<td>0.77</td>
<td>4.67</td>
<td>0.99</td>
<td>0.86</td>
<td>3.58</td>
</tr>
<tr>
<td><strong>Min</strong></td>
<td>0.05</td>
<td>0.16</td>
<td>0.87</td>
<td>0.50</td>
<td>2.90</td>
</tr>
</tbody>
</table>

#### 4.2.8 PLAN CONFORMITY FOR AVM

For the AVM the most of CCI values range between 0.50 and 0.80 see Table 10 and Figure 24. The median and mean values are comparable and this implies that the number of volumes is quite evenly distributed. The values for CCI are quite low and this is due to the fact that many of the observed AVMs are larger than the average volume. For a perfect score the size, shape and position of the observed volume must coincide with the average volume. The lowest score of the CCI for AVM is measured for the volume that is the smallest of them all. In this plan a high DCI is calculated as illustrated in Figure 25. The DCI of this plan are the result of 75% of the average target missed and this is mainly due to the small volume. Some of the observers do not agree with the choice of imaging methods and state that the delineation of the target is speculative. This may result in delineating larger volumes to make sure the whole lesion is included. The CI calculations resulted in almost as low mean value as for astrocytoma but the significance is difficult to interpret. One value is 0.79 and as well coupled with the lowest score of the PCI which is 0.75 as shown in Figures 26 and 27. Five of the observers did not contour the target and no PCI indexes could be scored for these plans. Overall, the results for the PCI are high in all plans where a structure was contoured as
illustrated in Figure 27. The complexity of the shape of this target is lower than for astrocytoma and vestibular schwannoma, the disagreement lies instead in the location of target. This is the fact that could be clinically significant. The GI is lower than the approved upper limit of 3 in almost all plans, for the rest being just above 3 as shown in Figure 28. The volumes of all delineated targets are relatively high for the treatment with LGK and this requires a steep dose fall-off and would result in a relatively low value of the GI.

Table 10. Plan conformity indexes for AVM.

<table>
<thead>
<tr>
<th></th>
<th>AVM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Concordance Index (CCI)</td>
</tr>
<tr>
<td>Mean</td>
<td>0.63</td>
</tr>
<tr>
<td>Median</td>
<td>0.65</td>
</tr>
<tr>
<td>Max</td>
<td>0.81</td>
</tr>
<tr>
<td>Min</td>
<td>0.24</td>
</tr>
</tbody>
</table>
Figure 24. Bar-graph illustrating the CCI for all four disorders. The y-axis represents the CCI value.

Figure 25. DCI for all four disorders, normalized to the average volume. The y-axis represents the fraction of average volume not included in each case.
Figure 26. Bar-graph illustrating the CI, the y-axis represents the CI value.

Figure 27. PCI for all four disorders. The y-axis represents the PCI value.
Figure 28. GI for all four disorders, y-axis represents the value of dose fall-off.

4.3 RADIOBIOLOGICAL ANALYSIS

4.3.1 TUMOUR CONTROL PROBABILITY
Calculation of TCP is based on several assumptions: average target is the real target, the model applied for cell survival works well for high doses of radiation, $\alpha/\beta$ and $\gamma$ parameters used are valid for the specific targets, the survival fraction at 2 Gy is 50% and each specific pathology and hence target has an infiltrative power into normal tissue depending on distance from the border of the average target. The TCP was then calculated for the average target assumed to represent the true tumor and the dose distributions received from the participating centers. The aim of the calculations was the assessment of the influence of misdelineation of the target and the resulting plan on the probability of controlling the tumor assuming that the cells that have to be eradicated are located within the average target and have infiltrated the normal tissue outside the average target according to their specific pathology. The average target structure is for all four brain disorders smaller and within the observed delineated structures. This implies that this target is subjected to a higher dose than the prescribed dose. The prescribed dose is 11 Gy at 50% isodose for meningioma. By looking
at the 50% isodose versus the average target one could observe that the target is positioned within
the isodose surface and by that is subjected to an overall higher dose. This is valid for all cases. This
results in that the target is exposed to a much higher dose, even at its boundaries.

The result of TCP for meningioma is 100% for the average target irradiated with the dose
resulting from the plans done for the observed targets. However, the dose distributed throughout the
whole structure, voxel by voxel was between 10 Gy and 22 Gy which is within the region where the
LQ model may not be accurate in predicting the survival. The result would give an underestimation
of the fraction of surviving cells which in turn would result in an overestimation of TCP. For
vestibular schwannoma and astrocytoma the result are the same, a TCP of 100% for the average
target and the dose distribution resulting from the plans done for the observed targets. The average
target for astrocytoma is to a great extent smaller than the observed delineated volumes and all dose
matrices will then result in high doses distributed through all voxels of the average target. The
radiobiological evaluation of the probability of controlling the tumor for meningioma, astrocytoma
and vestibular schwannoma resulted thus in a TCP of 100% for all three types of tumors. The level
of confidence on these calculated values depends on the accuracy of the models used for calculating
the TCP on one hand and on the validity of the parameters used in the models on the other hand.
Given thus the controversy in the literature regarding the use of the LQ model for predicting the
survival fraction of cells at doses above the levels currently used in conventionally fractionated
radiotherapy, i.e. 2 Gy per fraction, care should be taken in using it for predicting the outcome of
SRS. Furthermore, the difficulty in finding the scientific literature highly reliable and validated
parameters required by the TCP model might also raise questions regarding the relevance of the
results.

4.3.2 PROBABILITY OF AVM OBLITERATION

Probability of AVM obliteration for the observed and the average target is given in Table 11. The
calculated probabilities are extremely low and do not reflect the clinical reality. As for the TCP, the
results for probability of AVM obliteration are also heavily influenced by the choice of parameters
used in the model. The predictions of the treatment outcome from the radiobiological point of view
are thus highly questionable for the tumors and the AVM due to the fact that they do not seem to
reflect the clinical observations, the main reason probably being the lack of reliability on the
radiobiological parameters found in the literature and used in the calculations.

However, the work performed in this project resulted in preparing the theoretical frame and the
supporting software for the evaluation of the LGK treatment plans in terms of probability of
controlling the brain disorder when accurate radiobiological parameters would become available.
Table 11. AVM obliteration probabilities.

<table>
<thead>
<tr>
<th>Observer</th>
<th>Obliteration probability [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed Target</td>
</tr>
<tr>
<td>1</td>
<td>0.31</td>
</tr>
<tr>
<td>2</td>
<td>0.15</td>
</tr>
<tr>
<td>3</td>
<td>3.50</td>
</tr>
<tr>
<td>4</td>
<td>0.22</td>
</tr>
<tr>
<td>5</td>
<td>0.53</td>
</tr>
<tr>
<td>6</td>
<td>0.82</td>
</tr>
<tr>
<td>7</td>
<td>0.08</td>
</tr>
<tr>
<td>8</td>
<td>0.05</td>
</tr>
<tr>
<td>9</td>
<td>0.74</td>
</tr>
<tr>
<td>10</td>
<td>0.22</td>
</tr>
<tr>
<td>11</td>
<td>11.83</td>
</tr>
<tr>
<td>12</td>
<td>1.89</td>
</tr>
<tr>
<td>13</td>
<td>2.35</td>
</tr>
<tr>
<td>14</td>
<td>0.11</td>
</tr>
<tr>
<td>Mean</td>
<td>1.63</td>
</tr>
<tr>
<td>Median</td>
<td>0.42</td>
</tr>
<tr>
<td>Max</td>
<td>11.83</td>
</tr>
<tr>
<td>Min</td>
<td>0.05</td>
</tr>
</tbody>
</table>

4.3.3 RISK OF SECONDARY CANCER

The risk of inducing cancer in the normal tissue outside the tumor based in the calculations in this study is shown in Table 12 and in Figure 29 for all four brain disorders. This is calculated by Equations 7 and 8. Figure 30 shows the risk of secondary cancer in the normal brain outside the target as a function of the volume of the observed target. As could be observed there is a trend in
increasing the risk with the treated volume. The largest risk of secondary cancer is expected according to the calculations for AVM where both the mean and median value is higher than 1%. This is as well the one case where the mean and median volume delineated is largest. For astrocytoma the most of the calculated values for risk are below 1.5% except for two higher values of 2.6% and 3.0%. The median value is in this case a more reliable measure of the risk and the value is below 1% and comparable with the risk for both meningioma and vestibular schwannoma. No account is taken for the previous fractionated treatment of astrocytoma and the cells radiation sensitivity post treatment. The sensitivity to radiation for vestibular schwannoma after surgery could as well be altered. The vascular properties of the tissues surrounding the surgical resection are not investigated. For meningioma the mean and median values of the risk are similar, indicating that the calculated risk values are evenly distributed around the mean. Risk for secondary cancer is a quantity which not includes the sensitivity of individual patients to radiation, as well as previous treatments such as other forms of RT, drugs or craniotomy. This type of regard is difficult to incorporate into a mathematical model.

Table 12. Risk of secondary cancer.

<table>
<thead>
<tr>
<th></th>
<th>Astrocytom</th>
<th>Meningiom</th>
<th>Vestibular Schwannoma</th>
<th>AVM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>1.12</td>
<td>0.90</td>
<td>0.86</td>
<td>1.07</td>
</tr>
<tr>
<td>Median</td>
<td>0.88</td>
<td>0.89</td>
<td>0.93</td>
<td>1.11</td>
</tr>
<tr>
<td>Max</td>
<td>3.01</td>
<td>1.21</td>
<td>1.05</td>
<td>1.40</td>
</tr>
<tr>
<td>Min</td>
<td>0.54</td>
<td>0.69</td>
<td>0.20</td>
<td>0.54</td>
</tr>
</tbody>
</table>
Figure 29. Bar plot illustration of the risk of secondary cancer for all four brain disorders. The y-axis represents the percentage risk.
Figure 30. Risk versus volume delineated for (a) anaplastic astrocytom (b) meningiom (c) vestibular schwannoma (d) AVM. Y-axis represents risk in percent and x-axis represent target volume delineated in cm$^3$. 
5 CONCLUSIONS

The purpose with this study was to evaluate the inter-observer differences in target delineation and to evaluate the radiobiological outcome in probability of controlling the target and risk of secondary cancer. The analysis of the delineated targets was based on a calculated average target structure which is assumed to resemble a true target if all observers delineate with the same clinical demands. These demands were given to the observers as general instructions with the purpose of minimal influence on the clinical work. The construction of the average target was shown to be highly influenced by the large differences in target volume which also influenced the statistical analysis of volume and radiobiological outcome. Conclusions are that differences between observers in target delineation for these four brain disorders appear to be clinically significant. A module allowing the evaluation of the plans from the radiobiological point of view for different target delineations was developed. The probability of controlling the tumor for the meningioma, astrocytoma and schwannoma, and the probability of AVM obliteration respectively were calculated based on the data available in the literature regarding their sensitivity to radiation. The invasive character into the normal tissue of the specific pathologies was also taken into account in the calculation of the tumor control probability. With respect to the irradiation of the normal tissue outside the target, the risk of developing secondary cancer after stereotactic radiosurgery was also evaluated. This thesis presents thus the frame for dosimetric and radiobiological evaluation of the Leksell Gamma Knife® Perfexion™ plans taking into account the differences in delineating the target between various observers which has the potential of being a useful tool for clinical stereotactic radiosurgery.

The many choices for observers in the treatment planning process contribute largely to the disparities in target volume, shape and location for all disorders included in this study. A broader usage of radiotracers/PET, spectroscopy or diffusion tensor imaging in the treatment planning could be applied to better identify the metabolically active tumor tissues. It was however beyond the scope of this paper to further discuss the clinical use of these more advanced functional imaging approaches.
6 FUTURE WORK

The interest in the future studies will be focused on inter-observer differences for other brain disorders and with this, disorders of a general reduced complexity and to evaluate the variations in contouring philosophies. Observers in this study were given minimal amount of instructions for the minimal influence on the clinical work. This resulted in many factors contributing to the discrepancies in average target calculation. Future studies could include the variations in prescribed dose for one particular target and to estimate the variations related to this factor. This should include a model predicting the survival fraction at doses of concern in stereotactic radiosurgery and reliable parameters. The framework for a new analysis is already done. Another aspect which is not included in this study and should be further explored is probability of secondary cancer calculated for the average target and the comparison with the results of this study.
ACKNOWLEDGEMENTS

First of all I would like to thank all my supervisors at Karolinska Hospital in Stockholm and Elekta Instrument AB in Stockholm. Thank you Iuliana Toma-Dasu from the department of Medical Radiation Physics at Stockholm University and Karolinska Institute for assisting me with necessary steps in the radiobiological calculations and input on interesting articles. You have always given me the time and given me good input on the written report. Thanks to Håkan Nordström and Jonas Johansson for all tips on shortcuts and tricks in MATLAB and with ideas in the part of structure and volume. Thank you Per Kjäll for inputs on the structure of the written report and discussions on future projects. I am thankful for the positive inputs on my ideas for the project and to always giving me time for discussion. I would also like to give my appreciation to Björn Somell at Elekta Instrument AB for showing a large interest in my work. Also, the help with anonymization and removal of original plans before distributing these indications around the world I have Björn to be thankful to. Anna Friebe at Elekta helped with the identification of dose matrices and ideas for size adjustment of these. All persons willing to participate in this study I give an extra large thanks to, I appreciate the time taken for my project and the large interest shown. Last I wish to acknowledge the source of the cases used in this study, thank you for your willingness to send me these indications on the preferences given.
BIBLIOGRAPHY


APPENDIX 1. GENERAL INSTRUCTIONS

RECURRENT ANAPLASTIC ASTROCYTOM

45 year male
- Presented with headache, nausea and vomiting in March 2004
- Lt. thalamic anaplastic astrocytoma was found and totally removed in April 2004.
- 72Gy of extended local radiation by accelerated hyper-fractionation method and chemotherapy (ACNU) prevented recurrence until April 2009.
- Recurrence at contra-lateral thalamus.
- Caudal and medial temporal lesions are treated by Gamma Knife.

In this patient, methionine-PET was available and the dose plan originally made was based on a mixture of T1(+), FLAIR, and PET. The latter is a matter of choice, if it is in clinical use at your site.

**Target matrix:** X: 87.4
Y: 103.5
Z: 104.0
Grid Size [mm]: 2.2

**Dose:** 32 Gy at 100%, 16 Gy at 50%

**Image studies** used in original treatment plan are distributed here:

2010-05-30: - cor+ MR coronal orientation, co-registration to txcor+, 24 images.
- sag+ MR sagittal orientation, co-registration txax+, 21 images.
- ax+ MR axial orientation, co-registration to txax+, 21 images.
- axFL MR axial orientation, co-registration to txaxfl, 21 images.
- ax- MR axial orientation, co-registration to txax+, 21 images.
- axT2 MR T2W axial orientation, co-registration to txaxfl, 21 images.
- PET1 PT axial orientation, co-registration to txax+, 17 images.
- PET2 PT axial orientation, co-registration to txax+, 35 images.

2010-06-18: - txaxfl FLAIR MR axial orientation, 38 images.
- txcor+ MR coronal orientation, 86 images.
- txax+ MR axial orientation, 80 images.
LATERAL CAVEROUS SINUS MENINGIOMA
- 75 year female
- Presented with III and VI nerve palsy (diplopia and blepharoptosis).
- Dose to the part of the tumour most proximal to rt. Optic nerve was decreased

Target matrix: X: 85.7
Y: 122.1
Z: 125.1
Grid size [mm]: 1.3

Dose: 22 Gy at 100%, 11 Gy at 50%

Image studies used in original treatment plan are distributed here:
2010-01-15: - txcor+ MR coronal orientation, 18 images.
- txax+ MR axial orientation, 18 images.
- txcorT2 T2W MR coronal orientation, 18 images.
- CT Axial orientation, 40 images. (Fusion of txax+ and CT)
- FA Fusion of txax+ and CT

OPERATED LATERAL VESTIBULAR SCHWANNOMA
- 61 year male
- Present with ataxia
- 90-80% of tumour surgically removed 3 months prior to GKRS
- Deaf, slight diplopia due to VI palsy, slight facial palsy and facial hypesthesia.

Target matrix: X: 120.0
Y: 86.7
Z: 132.4
Grid size [mm]: 1.6

Dose: 24 Gy at 100%, 12 Gy at 50%
Image studies used in original treatment plan are distributed here:

2010-02-04:  - precorFIESTA+  MR coronal, co-registration with CT, 40 images.
              - preaxFIESTA+  MR axial, co-registration with CT, 40 images.
              - preax+  MR axial, co-registration with CT, 40 images.

2010-02-05:  - txax-  MR axial orientation, 40 images.
              - CT  Axial orientation, 40 images.
              - FAFIESTA  fusion of preaxFIESTA+ and Ct

LATERAL FRONTAL AVM

- 39 year male
- Presented with twitching of tongue. No past history of bleeding.

Target matrix:  X: 148.2
               Y: 96.5
               Z: 81.3

Grid size [mm]: 1.6

Dose: 32 Gy at 100%, 16 Gy at 50%

Image studies used in original treatment plan are distributed here:

2009-03-17:  - TxTOF-  Time Of Flight, MR axial orientation, 80 images.
              - TxT2  MR axial orientation, 22 images.
              - TxT1-  MR axial orientation, 12 images.
              - TxT1+  MR axial orientation, 18 images.
              - TxTOF+  Time Of Flight, MR axial orientation, 80 images.

Treatment plans should be made based on some criteria:

- Taking the patients eventual treatment history into account,
- Write down some of the aspects to consider in the planning process,
- Adjust matrix as given above (for our ability of comparison),
- Indicate target structures,
- Indicate critical structures (optional),
- Report dose-rate at your LGK at time of planning,
- Set dose as given in individual case,
- Treatment plans according to normal procedure at your site,
- Plans made by one of the traditional treatment planner/planners at your site (if possible),
- In other words, we wish to have plans that resemble a clinical reality as much as possible.
- All pathology will be distributed in the image series given.
- This is not an evaluation of individuals; reason for several requests at the same site is to receive as many cases as possible. Therefore, I ask you to not discuss your work with each other.
- I will conclude this study in the end of May 2011, please let me know if you need more time.
APPENDIX 2. REFLECTIONS BY OBSERVERS TO TREATMENT DATA

In the general instructions given to all observers together with LGK data the general request of feedback on the parameters for treatment setup as well as some general thoughts on the four brain disorders was included. The overall perception of all four brain disorders was that they were highly complex. This resulted in several disagreements between centers regarding both treatment setups and the validity of treating with LGK at all. All brain disorders were reported to generate an unusually large amount of shots for the coverage of the complex target structure. Two planners reported problem with the delineation of structure as they were not able to draw them. They planned instead manually using isodose lines for target and risk structures. Another group of observers reported that the initial delineation of target structure is not of common practice at their site. They also planned with the isodose lines as guide for a satisfactory plan. Here is a summary of different approaches to the brain disorders investigated in the present study. It has to be emphasized that these are the approaches that differ from those following the given instructions while the majority of observers fully agreed on the approach suggested in the instructions.

ANAPLASTIC ASTROCYTOMA
Anaplastic astrocytoma was not considered as a suitable case for SRS with LGK by the majority of planners. This is both due to the histology and placement of lesion and due to the fact that the patient received a high dose of radiation two years ago. One observer viewed the participation as purely an exercise because of the non agreement both to the validity for treatment and the peripheral dose setting. The planners which disagreed on the validity of this case for GK treatment still performed a plan as if they were to treat the patient which makes the plan legitimate to include in the study. LGK is usually used in the treatment of recurrent malignant glioma where the recurrence is focal and has a location which makes surgical resection not suitable. The proposed case is a recurrence of malignant glioma, previously treated. There are two reasons reported by one observer for determining the case non typical for being treated with LGK. First it involves two areas of recurrence, a multi focal appearance. Secondly, the original low grade glioma is likely to have transformed in multiple spots within the background. The result of this is two areas of high grade glioma surrounded by a background likely to represent lower grade gliomas. The treatment of this collection of lesions thereby becomes heavily complex and involves two different dose prescriptions. This was in fact observed in some of the received plans where the planner delineated two structures involving high and lower contrast regions. The 50% isodose and the 25% isodose
were then fitted to these structures. These plans are not optimized with respect to the dose fall-off but reflect a highly complex treatment planning method. The prescribed dose was suggested to be increased by a group of observers. Another source of discrepancy between plans was the availability of two PET images. It is not of practice to plan with the information from PET at all sites involved in this study and therefore the target volume differed greatly. The observers which incorporated the PET images in the treatment planning delineated a larger target structure. A few observers delineated a suspected structure with the help of PET but this was not incorporated in the plan. In many of these cases a larger grid size was suggested or employed to cover the entire lesion. The target matrix was set up with a large grid size; another matrix set up was suggested as several dose matrices put together, due to the multi-targeting of the lesion involved. Another method applied by planners was to reduce the size of the matrix, still using one matrix. These observers were not taking into account the PET image and therefore the target and the matrix were smaller. One observer estimated the patient’s risk of radionecrosis to about 20%. Another observer also included a nodule on the left side, the main two lesions being located on the right. The method of sector blocking was in many of the plans applied to keep the dose to the optic nerves below critical value. Hypo-fractionated SRS was suggested as an alternative treatment for this disorder. Finally, the general comments were that the majority of observers are not fully satisfied with their plans or in other words, that a more conformal plan could have been performed with other LGP settings. This is of course due to the many different suggestions on how the planning process could have been altered.

MENINGIOMA

The meningioma was classified as both fairly representative and highly complex for treatment planning with LGK. This disorder was reported as the only typical case for radiosurgery amongst these patients by some planners. Majority of observers delineated the optic pathways as critical structures as they are in the closest proximity to the lesion. A FLAIR-MRI sequence was proposed for being used for the location of the optic apparatus relative the lesion. This was not included in the image modalities for this case. Some planners reported that the coverage of target had to be compromised to be able to keep the dose below the limit for these OAR by shielding the beams in the directions passing the optic pathways. This is performed with sector blocking but the method is not effective for the optimization of dose fall-off in the Z-direction. A way of planning reported when a critical structure is as nearby as for this disorder is to first plan the tumor to the prescription dose and adjust the shots that affect the optic apparatus. This further limits the target dose only at the tumor-target interface. By this, a higher dose may be delivered to the target at all angles that not
interfere with the critical structure. For several angles, the peripheral dose to target is lowered with an optimal critical structure sparing. The optic apparatus (optic nerves, optic chiasm and optic tracts) were reported as the dose limiting structure for this disorder. The risk for patient to develop right eye ambliopia\textsuperscript{9} was very high. A higher prescribed dose was suggested by some observers in order to partially compensate for the shielding. Another suggested fractionated RT as treatment option for this patient due to the over-irradiation of the optic pathways instead of lowering the dose. Many of the planners had to adjust the target matrix’s center point and the grid size of it to be able to cover all of the target structure. These changes were in many plans small but still contributed to a large complication in the volume statistics calculations. Majority of the observers reported an enlargement of the target matrix. Another group of observers reported that the dose settings given for this disorder were to low and instead an increase of 2-5 Gy depending on volume and nearby critical structures. The age of the patient is also a limiting factor for SRS. The somewhat old age suggests that it should be demonstrated that the tumor is actually growing before decision on intervention.

VESTIBULAR SCHWANNOMA

The apprehension of planning for vestibular schwannoma is of the same character as with the astrocytoma. It is a difficult and complex target to construct a plan. Therefore for both gradient index and conformity index value lower than the optimal was expected due to the asymmetric shape of the lesion. Since the patient already suffers from diplopia and facial palsy, a lower prescribed dose was suggested. The delineated critical structure included the brainstem and cochlea. This was not done by all observers since it was not in the proximity of the lesion and would receive a low dose. The cochlea was not proposed to be of concern for this case since the patient had lost the hearing on the left side. This resulted in a somewhat higher dose suggested when no regard was taken to the cochlea. No information was given about the pre-surgical lesion. Some observers have requested it as it would be useful to discern the post-operative changes versus growing tumor. The timing of imaging was commented on. This could eliminate any uncertainty associated with the co-registration of images despite the appearance of this disorder to be slow growing. It is always of a high importance to minimize the time between image acquisitions before treatment to that on the day of treatment with the stereotactic frame attached. The choice of MRI sequences for the pathology was not reported as optimized by one planner. This is of course one of the basics in the planning process and it differs between observers. Many observers were reluctant to believe that 90\% of the tumor has been surgically removed 3 months prior to SRS. The target matrix was

\textsuperscript{9} Known as lazy eye, a reduced vision which is not correctable by glasses or contact-lenses.
divided into several targets by some planners due to the fact that the residual tumor after craniotomy was so complex.

**AVM**

The prescription dose to AVM was some source of disagreement and a higher dose was suggested at some sites. Both the suggestion to a higher dose and the complete disagreement to the dose given in instructions are reported. It was highlighted as well that the AVM was only a superficial lesion and an expert neurosurgeon should be able to successfully treat it by surgery followed by an endovascular embolization\(^9\). The treatment volume was larger than necessary due to that the target was hidden amongst the monstrous vessels on angiography. The coverage of the AVM then becomes speculative to a large extent and treatment volume is increased for the treatment to be valid. Several planners report problems with identifying the nidus on angiography. With the use of MRI the target volume was overestimated. Suggested solution for a large volume to be treated with SRS is to divide the treatment into two sessions; treating half the volume in one session and bringing the patient back after 3-6 months for next session. Some observers said, due to the non history of bleeding, that this lesion should not be treated at all and again that a microsurgical approach is advantageous compared to SRS. In several plans the grid size of the target matrix was increased to include the whole lesion. One planner reported that it was not possible to draw the target structure before planning.

\(^9\) A procedure to fill / close blood vessels, used to treat hemorrhage.