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The role of radiosurgery for the management of benign intracranial meningiomas

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This work is dedicated to Jule

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Summary

BACKGROUND: Radiosurgery is the main alternative to microsurgical resection for benign meningiomas.

OBJECTIVE: To assess the long-term efficacy and safety of radiosurgery for meningiomas with respect to tumor growth and prevention of associated neurological deterioration. Medium- to long-term outcomes have been widely reported, but no large multicenter series with long-term follow-up have been published.

METHODS: From 15 participating centers, we performed a retrospective observational analysis of 4565 consecutive patients harboring 5300 benign meningiomas. All were treated with Gamma Knife radiosurgery at least 5 years before assessment for this study. Clinical and imaging data were retrieved from each center and uniformly entered into a database by 1 author (A.S.).

RESULTS: Median tumor volume was 4.8 cm3, and median dose to tumor margin was 14 Gy. All tumors with imaging follow-up < 24 months were excluded. Detailed results from 3768 meningiomas (71%) were analyzed. Median imaging follow-up was 63 months. The volume of treated tumors decreased in 2187 lesions (58%), remained unchanged in 1300 lesions (34.5%), and increased in 281 lesions (7.5%), giving a control rate of 92.5%. Only 84 (2.2%) enlarging tumors required further treatment. Five- and 10-year progression free survival rates were 95.2% and 88.6%, respectively. Tumor control was higher for imaging defined tumors vs grade I meningiomas (P< .001), for female vs male patients (P < .001), for sporadic vs multiple meningiomas (P< .001), and for skull base vs convexity tumors (P < .001). Permanent morbidity rate was 6.6% at the last follow-up.

CONCLUSION: Radiosurgery is a safe and effective method for treating benign meningiomas even in the medium to long term.

KEY WORDS: Control rate, Follow-up, Meningiomas, Multicenter study, Radiosurgery

List of abbreviations

RS: Radiosurgery

SRS: stereotactic radiosurgery

RT: radiotherapy

WHO: World Health Organisation

GK: Gamma Knife

CK Cyber Knife

LINAC: linear Accelerator

Gy: Gray

Co^{60}: $Cobalt^{60}$ radio nuclide

MV: Mega Volt

cm: centimetre

cm^3: cubic centimetre

cc: cubic centimetre

CNS: central nervous system

TNM: TNM Classification of Malignant Tumours

CT: Computer Tomography

MRI: Magnetic Resonance Imaging

AVM: artero-venous malformation

SFRT: fractionated stereotactic Radiotherapy

IMRT: intensity modulated Radiotherapy

ASTRO: American Society for Radiation Oncology

EGKS: European Gamma Knife Society

EBRT: external Beam Radiotherapy

ARIE: adverse radiation imaging effects

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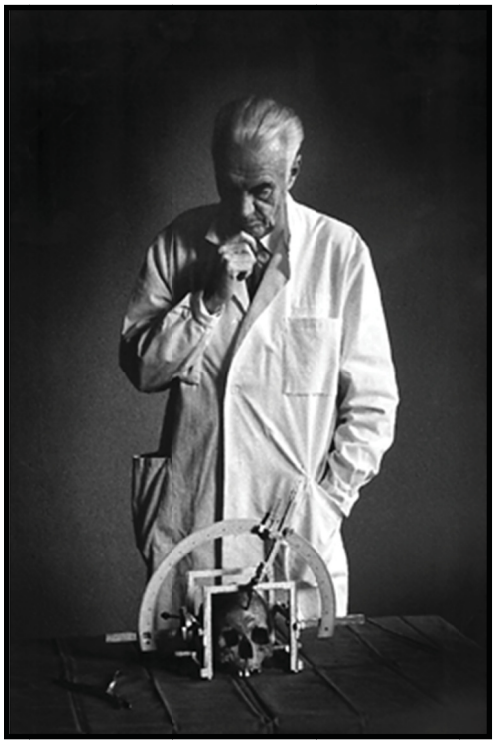
1 Introduction



“Tools used by the surgeon must be adapted to the task and where the human brain is concerned no tool can be too refined.”

Lars Leksell MD

“Radiation is a gift of God but physicians using it are only human beings”

Jonathan Knisely MD
(Personal communication to Antonio Santacroce)

1.1 Foreword

With these citations I would like to start my dissertation about the treatment strategies of benign intracranial meningiomas giving particular attention to the role of stereotactic single session highly conformal radiation therapy also called “radiosurgery”.

In the heroic era of neurosurgery the complete resection of intracranial lesions was surely the most intriguing challenge for a surgeon. The avid enthusiasm shown by many pioneers of this medical area from Cushing to Yasargil from Davidoff to Al Mefty, brought to dramatically development of clinical indications, diagnosis, and of course surgical technique to achieve a complete tumour removal.

Nevertheless anatomy and biology of meningiomas are complex as the possible treatment options themselves. In his pioneer work penned in 1938 Harvey Cushing writes “for the surgeon to know from the clinical history and examination of the patient just what is likely to be encountered is highly advantageous; but it’s equally important to foretell what its future behaviour will be, however treated” (Cushing et al., 1938). These remarks remain pertinent today as they were at that time.

In early 90’s Al-Mefty pioneer of meningioma microsurgery writes “A meningioma is in many ways the soul of neurosurgery. The progress in meningioma treatment mirrors advances in neurosurgery, while advancements in neurosurgery are to put to maximum use to improve the treatments of meningiomas (Al-Mefty, 2011)

Once more Cushing many years before him wrote: “there is today nothing in the whole realm of surgery more gratifying than the successful removal of a meningioma with subsequent perfect functional recovery….the difficulties are admittedly great, sometimes insurmountable and though the disappointments are many, another generation of neurological surgeons will unquestionably see them largely overcome” (Cushing et al., 1938).

The last 20 years confirmed the statements above.

1.2 The matter of clinical debate

A Growing number of clinical reports show how meningiomas represent a very intriguing oncological entity and a challenge in the field of brain tumours either for their diagnosis as well as for the therapeutics strategies to choose (Santacroce et al, 2014).

The management of benign meningiomas is still a strong matter of debate among physicians. (Santacroce et. al 2014) Microsurgical removal including dural tail and underlying bone sit still the gold standard for benign meningiomas. According to the standards of modern neurosurgery a surgical "cure" WHO Grade 1 meningioma, as benign tumour, can be accomplished (Santacroce et al., 2014).

The management of benign intracranial meningiomas is evolving very quickly. The refinement of microsurgical techniques is just one of the major issues to consider. More generally the optimal management of benign meningiomas either histologically confirmed WHO Grade I or defined by a simple MRI is based on a multidisciplinary approach considering the various treatment options and tools available in the modern era of medicine a requiring the experience of the most various physicians from the neurosurgeon to the ENT skull-base surgeon from the neuro radiologist to the radiation oncologist.

From the historical perspective radical surgical resection was this first goal to achieve tumour removal while preserving the patient from any kind of complication. As alternative a so called "active surveillance" was the second treatment choice for asymptomatic non operable benign meningiomas (Nakamura et al., 2003, Niiro et al., 2000, Olivero et al., 1995)

The landmark contribution of Donald Simpson (Simpson, 1957) reporting the recurrence rate of benign meningiomas according to the degree of microsurgical removal. most of the deep located intracranial meningiomas, benign in particular, are not amenable to a Simpson Gr. 0 resection due to a simple and rather intuitive anatomic reason: a removal of dural tail with 2 cm margins of dura mater, even for the most experienced operator, is not possible without exposing the patient to an unacceptable risk of perioperative morbidity/mortality. If we

assume for those tumours a lower degree of resection a recurrence rate of 9–40 % is reasonably predictable (Santacroce et al., 2014).

In the pioneering era of neurosurgery many advances have been done with respect to better operative techniques, introduction of intraoperative microscope, intraoperative monitoring and neuronavigation systems. According to the pioneering work of Al Mefty (Al-Mefty et al., 2011) some predictive factors are to be considered in pursuing safe an total removal of benign meningiomas, which may be divided in pure surgical– bony invasion, Simpson grade of resection, skull base approach selected to reach optimal tumour exposure and pure oncological – histology, pathological anatomy, arachnoidal dissection and cytogenetic features (Santacroce et al., 2014).

Parallel to the development of microsurgery, radiation techniques of the central nervous system have seen, over the twentieth century a tremendous evolution. This was achieved thanks to the simultaneous development of radiation oncology concepts and the raising era of stereotactic/functional neurosurgery. Lars Leksell was surely the first person representing the convergence of these two disciplines. Applying under the use of stereotactic frame based coordinates a single high dose of photon radiation to a small volume was defined in early 1960s the term of stereotactic single session highly conformal radiotherapy also called “Radiosurgery”. The development of this technique gives to physicians another way to pursue a safe management of meningiomas. Its role became very soon well established for vestibular schwannomas but is nowadays matter of debate between physicians, from one side microsurgeons claiming that complete surgical removal is ought to be the first main goal to reach, despite the risks, and claiming the “danger” that radiosurgery may have in the medium to long term. On the other side its role is also discussed by many radiation oncologists preferring dose fractionation supported by radiobiological concepts defining the brain as “late responding tissue” to radiation exposure and thus, with a prolonged dose fractionation protected by arising of late side effects (Santacroce et al., 2014).

1.3 Radiosurgery – historical Background

The Conception of radiosurgery for intracranial target volumes goes back to the late 60's and follows a different development compared to conventional radiation therapy. As detailed by Backlund a historical background on stereotactic radiosurgery might be given first by describing the efforts of the pioneers of this field and second by describing the equipment and devices available for radiosurgery (Backlund, 2009). The idea of intracranial highly conformal radiation therapy for the central nervous System is not new and goes back to 1940 (Backlund, 2009).

At that time stereotactic surgical introduction of solid and liquid radioactive sources in the brain was a routine procedure for brain tumours in eloquent areas. Soon after the idea of using external cross firing of intracranial targets by narrow high energy ionizing beams took the place of those more invasive techniques while showing comparable or even better dose distribution and field parameters (Backlund 2009).

Historically developed by the stereotactic neurosurgeon Lars Leksell together with the physicist Börje Larsson, whose initial concept was for the management of functional neurologic disorders, the number of clinical indications has increased greatly. (Santacroce et al., 2014). Conversely to already existing photon based conventional dose fractionated radiotherapy, the first efforts of Leksell to perform radiosurgery, were made with particles with charge and given mass (ions). The idea was to use multiportal proton irradiation techniques taking advantage from the depth dose profile and the so called "Bragg Peak" (Larsson et al., 1958) (Backlund 2009).

Although devices used for particle radiotherapy, for example a cyclotron, could not be used in clinical routine of a single session highly conformal radiation due to the costs of the fournitures and challenging dosimetry, gave rise to the modern definition of radiosurgery. Through this experience and his neurosurgical background Leksell had the intuition to develop a device based on photon gamma radiation delivered with support of a stereotactic

frame based system with a large number of Cobalt 60 sources distributed in a half sphere around the patient's head collimated as much conformal as possible to a defined intracranial target volume.

The first clinical indications were primarily functional (thalamotomy capsulotomy) then within few years extend to oncological indications. Today, radiosurgery has today a well-established role for the treatment of small volume brain lesions like AVM's schwannomas in particular vestibular schwannomas, and an emerging importance for small remnants recurrent WHO Gr.I meningiomas, imaging diagnosed meningiomas and in more recent times also in the field of functional disorders such as trigeminal neuralgia, pharmacological resistant epilepsies etc.(Santacroce et al 2014).

It became soon very clear that the radiosurgery in clinical setting was somehow far away from the classical radiobiological clinical and oncological principles endorsed in classical radiation oncology. In Backlund's words "From a conceptual standpoint it became quite clear that basic key words for genuine clinical radiosurgery were (1) heavy single dose (2) small irradiated volume (3) benign pathology (4) functional surgery (5) stereotactic technique. Notably, involvement by any oncologist was deemed unnecessary. Corresponding key words for radiotherapy were 1) multiple dose/fractionation/radiosensitizers 2) larger volumes treated (3) malignancies and (4) an oncologists as principal of the treatment team (Backlund, 2009).

1.4 Radiosurgery for the central nervous system

According to a recent Review Radiosurgery can be defined as follows (Santacroce et al., 2013)

1) "the delivery of a single high dose of irradiation to a small and critically located intracranial volume through the intact skull"(Larsson et al., 1958)

2) “stereotactic radiosurgery: stereotactically guided delivery of focused radiation to a defined target volume in single session” (Niranjan and Flickinger, 2008)
3) “technique designed to deliver a high dose of focused radiation to a defined target volume to elicit a decide radiobiological response”(Niranjan and Lunsford, 2000)

More recently the American Society for Radiation Oncology ASTRO reached a consensus through a model policy which defines radiosurgery “discipline that uses externally generated ionizing radiation delivered in single session to eradicate or inactivate a target(s) in the head or spine without the need to make an incision defined by high resolution stereotactic imaging” (Seung et al., 2013, Santacroce et al., 2013).

The update of this slightly modified the consensus of definition of radiosurgery as follows: “Stereotactic radiosurgery (SRS) is a distinct discipline that utilizes externally generated ionizing radiation to inactivate or eradicate definite target(s) in the head without the need to make an incision.” (Seung et al., 2013). This avoids the delivery of a single session radiation under use of stereotactic coordinates for the spine.

Of note the latest consensus includes highly hypofractionated dose schedules as radiosurgery as follows: “SRS is strictly defined as radiation therapy delivered in one to five fractions via stereotactic guidance, with approximately 1 mm targeting accuracy to intracranial targets and selected tumours around the base of the skull.”

“The use of “stereotactic coordinates” in medical routine (from the Greek "stereo" (solid) and "taxis" (order)), implies the support of three-dimensional mapping techniques to perform a medical procedure” (Santacroce et al., 2014). According to the ASTRO the adjective “stereotactic” describes a procedure during which a target lesion is localized to a known three-dimensional reference system that allows for a high degree of anatomic accuracy. Examples of devices used in SRS for stereotactic guidance may include a rigid head frame

fixed to a patient, fixed bony landmarks, a system of implanted fiducial markers or other similar systems (Seung et al., 2013).

As already reported stereotactic coordinates systems might be used for radiation therapy and surgery in particular of the central nervous system.

It is important to underline the support of stereotactic systems to target a volume does not imply in every case a radiosurgery treatment. If the treatment is applied as high single dose-fraction, is defined radiosurgery, also named by many authors as stereotactic radiosurgery. If this radiation dose is delivered using more than one dose-fraction, always with support of stereotactic coordinates, is defined stereotactic fractionated radiotherapy. (Santacroce et al., 2014), Despite this clear definition the American radio-oncological community extended the definition of radiosurgery also to stereotactic hypofractionated treatments up to five fractions (Seung et al., 2013).

As previously reported goals of Radiosurgery are (Santacroce et al., 2013):

(1) exposure of a target volume to a single high dose of ionizing radiation which ultimately translates into a specific (toxic) radiobiological response(Niranjan and Flickinger, 2008)

(2) precise destruction of a chosen target containing healthy and/or pathological cells, without significant concomitant or late radiation damage to adjacent tissue (Kondziolka et al., 2007)

1.5 Radiobiology of Radiosurgery for the Central Nervous System

As already detailed in a previous chapter before radiosurgery was introduced a routinely used in clinical protocols, the delivery of a radiation dose in radiation therapy for cerebral lesions was usually performed by application of a variable number of dose fractions. The rationale of avoiding administration of a high single dose is the radiation exposure of the healthy nervous

tissue and therefore the risk of radio induced injuries associated (Santacroce et al., 2014)(Santacroce et al., 2013) .

Any radiation dose applied to a given tissue either normal or neoplastic causes a cascade of effects which are to be considered when performed in clinical/basic setting. This brings to definition of radiobiology as the field radiologic sciences that involve the study of the action of ionizing radiation on living things (Santacroce et al., 2014).

Every medical intervention aims to reach the highest rate of clinical successful outcome with the minimum rate of complications treatment related (Santacroce et al., 2014).

In classical conventional dose fractionated radiotherapy radiation dose is delivered applying a safety margin to include microscopic tumour infiltration in normal tissue (Santacroce et al., 2014). Usually a cumulative dose is delivered in a variable number of fractions, usually not more than 2Gy for standard fraction more than 2Gy for hypofractionation either in curative or in palliative setting (Santacroce et al., 2014). The cumulative dose is applied with 3D imaging simulation obtained with support of CT scan and MRI .

There is a clear relationship between time of radiation, dose and number of fractions with respect to biological effect on a given tissue is based on four basic principles of radiobiology defined as the "4Rs" of ionizing radiation in both clinical and biological setting (Elkind et al., 1965, Elkind and Sutton, 1960)(Santacroce et al., 2014)

- Repair: capacity of cells after sub-lethal damage radiation induced (Santacroce et al., 2013).
- Repopulation of surviving tumour stem cells during fractionated radiotherapy(Santacroce et al., 2013).
- Redistribution of cells between the cell cycle which after radiation injury in equally distributed radiation sensitive and resistant subpopulations(Santacroce et al., 2013).

- Re-oxygenation of hypoxic tumour cells after repeated radiation exposure. The radio-sensitivity of cells is inversely proportional to the hypoxic cell rate. The application of a dose fraction produces death of oxygenated tumor cells followed by oxygenation of hypoxic cells now more sensitive to the following dose fraction (Santacroce et al., 2013).

These four radiobiological principles are based on experimental evidences of application ionizing radiation to cell in vitro cultivated, for instance fibroblasts. (Elkind et al., 1965, Elkind and Sutton, 1960, Santacroce et al., 2013)

Together with clinical experience with three-dimensional conformal radiotherapy physicians could conclude that dose fractionation lessens the risk of injury of normal tissues and thus the rate of side effects (Hall and Brenner, 1993, Santacroce et al., 2013)

The relationship between desired outcome and undesired effect after radiation therapy can be conceptually represented by a sigmoid curve of a therapeutic window to achieve the better desired outcome (imaging control of the target volume) with lowest the rate of undesired outcomes (complication rate)(Niranjan and Flickinger, 2008)

By reducing the volume of tissue irradiated shifts dose-response curve for complications increasing the separation between cure and complication probability (Fig. 1)(Niranjan and Flickinger, 2008)

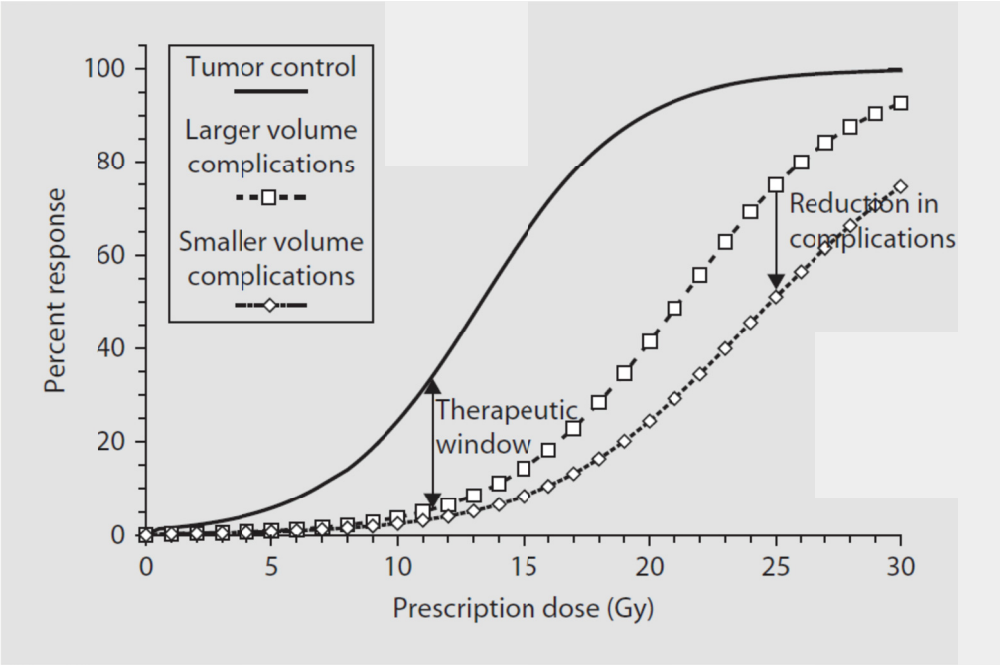


Fig. 1. Theoretical sigmoid dose response curves for tumor control with separate curves for complications with different treatment volumes. The two complication curves for radiation to a target with either a 15-mm margin and with no margin show how radiosurgery with no margin reduces complications for the same treatment dose (second arrow at 20 Gy pointing downwards). The complication curves shown were estimated from the RTOG radiosurgery dose-escalation data for brain metastases <2 cm in diameter (lower curve) and 3–4 cm in diameter (middle curve). Since more normal tissue would be irradiated when treating with a margin than treating a larger tumor, the middle curve most likely underestimates the complication risk.
(From A. Niranjan and J. C. Flickinger, "Radiobiology, principle and technique of radiosurgery," Progress in Neurological Surgery, vol. 21, pp. 32–42, 2008.) (with Permission)

The central nervous system (CNS) shows massively different oncological features if compared to other body parts (Niranjan et al., 2004). The TNM classification for malignant tumour cannot be applied (Santacroce et al., 2013). Furthermore distant metastases of primary brain tumours are very rare (Romero-Rojas et al., 2013). Furthermore The CNS reacts differently to ionizing radiation compared to other organs of the human body, implying that the radioresistance of brain tissue shows massively different features (Santacroce et al., 2013) Leksell investigated the effect of high dose focused radiation on the central nervous system more than 5 decades ago. His pioneering efforts he brain led to the definition of radiosurgery (Larsson et al., 1958, Steiner et al., 1980, Santacroce et al., 2013). We have already detailed about how assuming these considerations, the radiobiological principles used for dose

fractionation are not applicable for single session radiation (Niranjan et al., 2004, Kondziolka et al., 2007, Santacroce et al., 2013).

The radiobiological (toxic) effect of therapeutic radiation general aims to achieve the highest local tumour control and or improvement of survival; for benign intracranial meningiomas in particular local imaging tumour control is the first aim. Secondary aim is guarantee patient's safety by achieving the lowest complication rate treatment related. Conversely to malignant lesions, late response of healthy brain tissue to radiation is major issue for benign meningiomas, given the long term prognosis these tumour has. High dose conformity is therefore mandatory to achieve the lowest complication rate possible.

Mathematical Formalisms and models

Many models have been proposed to describe the biological response of a given tissue to radiation and dose fractionation schedule (Santacroce et al., 2014).

As already detailed The linear quadratic (LQ) model is so far the most used (Santacroce et al., 2014). Conceptually it describes the biological response of tissue in terms of surviving cell fraction (SF) to a given radiation dose (D) depending from a linear dose coefficient α for low doses and a coefficient for the square of the dose β for high dose fraction within a dose range from 1 till 8 Gy: biological effect is proportional to $\alpha D + \beta D^2$ (Santacroce et al., 2013):

$$SF = e^{-(a*D+\beta*D^2)}; \qquad (1)$$

Then

$$\ln SF = -\alpha D - \beta D^2. \qquad (2)$$

The extrapolated cellular survival curve describes a linear component of cell killing α and a quadratic component of cell killing β. The ratio of these two variables defines α/β ratio of a tissue and describes the point where the linear component α and the exponential component of

the survival curve β are equal or, in other words, it express the dose at which the two components of cell killing are equal (Santacroce et al., 2013).

The linear-quadratic formula is presently the standard way to mathematically represent the effect of radiotherapy to account for the effects of different fractionation schemes (Santacroce et al., 2013, Kondziolka et al., 2007) (Halperin et al., 2008).

According to this model is that normal tissues can be classified in:

- Early responding tissue (high α/β ratio)
- late responding tissue (low α/β ratio)

The central nervous system belongs to late responding tissues.(Santacroce et al., 2014)

On the contrary there is no clinical certain evidence about the α/β ratio of neoplastic tissue (Flickinger and Niranjan, 2008).

Furthermore, when performing radiosurgery, some limitations should be considered: (Santacroce et al, 2014).

- Some tumours show a considerable variation of α/β ratios despite their malignancy (Santacroce et al., 2014).
- Linear quadratic model cannot be applied with a dose of 8 Gy or more (Santacroce et al., 2014).
- The validity of the linear quadratic model has not been sufficiently investigated for very small target volumes (major diameter < 2cm) (Santacroce, Kamp et al 2014).
- many efforts to extrapolate a survival curve applying high doses to a benign lesions (<10 Gy) giving improbable values for which the risk of missing estimates of α/β ratios is too high, thus confirming the usefulness of such a model in radiosurgery (Flickinger and Niranjan, 2008) (Santacroce, Kamp et al 2014)

The consequence of these assumptions is that by increasing the fractionation schedule when treating slow growing tumours like benign meningiomas lesions no biological better response is to achieve.

Radiation doses of single session treatments are biologically equivalent to dose fractionation schedules. The clinical reason for dose fractionation is therefore sparing the surrounding healthy brain tissue from a high single dose of photon radiation when dose constraints of surrounding organ at risks cannot be achieved. Therefore highly conformal dose application is the key point in radiosurgery in order to spare dose exposure to surrounding tissue. Limiting factors of single session dose delivery are a close distance to organ at risks and the volume of the radiation target (Santacroce, Kamp et al 2014).

A number of experimental models have studied the effects of radiosurgery(Kondziolka et al., 2007). The magnitude of radiosurgical effects remain poorly understood, especially when described in terms of conventional radiation therapy doses. If we consider the application of radiosurgery for benign intracranial lesions like meningiomas, it has been observed that the radiobiological effect on meningiomas and other benign neoplasms is a combination of both cytotoxic and delayed vascular effects(Kondziolka et al., 2007, Santacroce et al., 2013).

After both vestibular schwannoma and meningioma radiosurgery they observed a doubling of the number of apoptotic cells after radiosurgery when compared to controls, within the first 48 h after irradiation. Many years ago it was reported that vascular effects played a secondary role.

In early nineties' the application of radiosurgery to the central nervous system has been classified into 4 groups with respect to target and surrounding tissue assuming the brain as late responding tissue with low alfa/beta ratio (Larson and Coffey, 1993, Larson, 1992, Loeffler and Larson, 1992)(Larson et al.,1992):

- late responding target embedded within late responding tissue: AVM
- late responding target surrounded by late responding tissue: meningioma/ schwannoma)
- Early responding target embedded within late responding tissue: low gr. Glioma
- Early responding target surrounded by late responding tissue: Glioblastomas/metastases

Today this oversimplified classification finds confirmation in the clinical routine of radiosurgery (Santacroce et al., 2014).

To conclude a recent report from the group of Pittsburgh gave clear indications about to radiobiological formalisms of radiosurgery drawing outcomes from radiobiological analysis of clinical data from radiosurgery (Niranjan and Flickinger, 2008):

(1) The linear-quadratic equation cannot reliably represent equivalent radiation effects when extrapolating from conventional fractionation (1.5–4 Gy per fraction) to high-dose (12–25 Gy) single fractions for radiosurgery (Santacroce et al., 2014).
(2) Mathematical models of radiation injury probability need to take into account that the target/tumor tissue's radiation response may affect the reaction of the surrounding normal tissue(Santacroce et al., 2014).
(3) The predominant radiation response of a radiosurgical target is mediated through the target or tumor vasculature. (Santacroce et al., 2014).

1.6 Epidemiology and histological features of meningiomas

As previously reported meningiomas account for approximately 13–26 % of primary intracranial and intraspinal neoplasms originating from the meningeal coverings of the brain

and the spinal cord. They tend to show predominance in women, with a female to male ratio of approximately 2:1 for intracranial and 10:1 for spinal (Marosi et al., 2008)(Santacroce et al., 2014).

The morphological features show that meningiomas are derived from arachnoidal (meningothelial) cells. The majority of meningiomas corresponds to grade I of WHO classification of CNS tumors and thus are benign, slowly growing tumors (Louis et al., 2007). Within the WHO Grade I group there are several subtypes, including meningothelial, fibrous (fibroblastic), transitional (mixed), psammomatous and angiomatous meningiomas. Grossly the majority of meningiomas are well demarcated solitary masses with a broad based dural attachment and smooth or bosselated surfaces. (Santacroce et al., 2014)

1.7 Radiation tolerance and response of Brain tissue after radiosurgery

1.7.1 Brain Parenchyma

Estimating the risks of radiation application with various dose schedules is a crucial part of dose treatment planning for both stereotactic dose fractionated and radiosurgery. Conversely to fractionated stereotactic radiotherapy the radiosensibility of the brain after radiosurgery shows massively different characteristics. Various structures of the brain react differently to a common radiation dose thus matter of evaluation before treatment (Santacroce et al., 2014).

Dose fractionation planning requires special attention usually to optic pathways (optic nerve and optic chiasma) and brainstem. The radiation tolerance of these structures is well known.

The risk of delivery of a high dose in single session might increase the risk of imaging and/or clinical complications. Variables to consider are the dose delivered and its distribution (isodose line), the volume of the tissue irradiated, the sensitivity of the tissue affected and history of any prior irradiation.

Flickinger proposed a model to predict permanent symptomatic postradiosurgery injury for AVM patients. (Flickinger et al., 2000, Flickinger et al., 1997): this revealed no difference in the likelihood of postradiosurgery injury imaging changes in different brain. Conversely dramatic clinical differences were seen with respect to neurological new symptoms or worsening neurological picture after radiation. These landmarks contribution suggest two conclusions: first an imaging change does imply a clinical worsening thus not requiring a further intervention. Second the indication to radiosurgical treatment should be given considering not only target volume the dose required and the contra indication to microsurgery operator's dependent but also the specific eloquence to ionizing radiation of the specific brain area. Flickinger described the effect of location on the risk of developing permanent symptomatic neurologic injury following arteriovenous malformation radiosurgery reported a higher risk injury to a given volume/dose for thalamus and basal ganglia followed by medulla, cerebellum temporal parietal and frontal lobe (Flickinger and Niranjan, 2008).

A prior history of dose fractionated radiotherapy to the same region of interest appears to have limited effects on the risk of developing post radiosurgery parenchymal edema with exception to the optic nerve (Flickinger and Niranjan, 2008)

1.7.2 Brainstem

Radiation tolerance of the brainstem represents one of major limitations when performing radiosurgery.

Sharma et al. conducted an analysis of patients with intra-axial brainstem lesions and documented the incidence of adverse radiation imaging effects (ARIE) and new neurological deficits after RS. Thirty eight patients harbouring 39 lesions either astrocytomas or AVM treated with GK RS in 6 year interval were evaluated. Brainstem exposure volume was calculated by subtracting the volume within the 12-Gy isodose line (12 Gray volume) from the prescription volume. ARIE was defined as anew parenchymal signal alteration on follow-

up magnetic resonance imaging sequences. The brainstem exposure at 12 Gy Isodose line was 2.03 cc. ARIE were reported in (18.4%) patients treated. ARIE correlated only with the presence of new neurological deficits and age younger than 40 years. 7.9% of patients developed minor residual deficits without any ARIE. No mortality was reported. The authors observed that exposure of the brainstem to more than 12 Gy at volumes as low as 0.1 cm3 can produce ARIE and therefore new neurological deficits (Fig. 2). The tolerance of the brainstem was related to patient age, target volume, and histopathology (Sharma et al., 2008) .

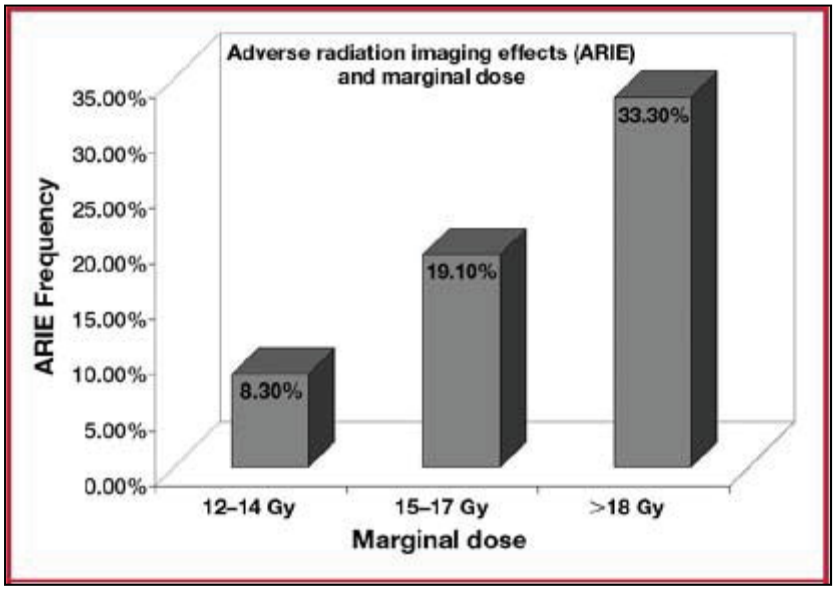


Fig. 2: Bar graph depicting a nearly linear rise in the incidence of adverse radiation imaging effects with an escalation in the marginal dose for benign intraaxial brainstem lesions.
Sharma, M. S., D. Kondziolka, et al. (2008). "Radiation tolerance limits of the brainstem." Neurosurgery 63(4): 728-732; discussion 732-723 (With permission).

1.7.3 Cranial nerves

The tolerance of cranial nerves is a crucial point in radiosurgery of benign meningiomas most particularly of the skull base.

According to clinical experience with radiosurgery and conventional fractionated radiotherapy sensory nerves appears to most sensitive, followed by somatic sensory nerves and motor nerves (Flickinger and Niranjan, 2008). The anterior optic pathways are the most dose

sensitive structures, implying that the dose delivered to the second cranial nerve should be always cautiously evaluated.

The first reports report a dose maximum tolerance of the optic nerve after radiosurgery to be at 8 Gy. More recent reports (Stafford et al., 2003) define maximal dose tolerance to be at 10 Gy may be related to better imaging technique available. The calculations of the biological effective dose of single session radiation compared to dose fractionation schedules to a given α/β ratio for the optic nerve of c.a. 1 tend to confirm 10 Gy as acceptable dose constraint. (Santacroce et al., 2014)

1.8 Histologic reaction of brain tissue to radiosurgery

Reaction of brain to tissue to fractionated dose radiation is well known and according to its radiobiological features to classify as late responding tissue (Santacroce et al., 2013, Kondziolka et al., 2007, Kondziolka et al., 2000, Kondziolka et al., 1999b, Linskey et al., 1993, Kondziolka et al., 1992a, Kondziolka et al., 1992b). When performing radiosurgery the reaction of the target and the surrounding brain tissue shows peculiar features.

The group from Pittsburgh analysed the histological feature of a sample of patients undergoing surgical removal of the target after failed radiosurgery which lead to tumor enlargement and clinical worsening. The histological changes after radiosurgery were classified as follows (Szeifert et al., 2009) (Szeifert et al., 2007, Szeifert et al., 2002a, Szeifert et al., 2002b, Major et al., 2002)

- Acute- within tumour target tissue connective tissue stroma and vessels resulting in sharply demarcated coagulation paremchymal necrosis nearly no stroma reaction dilatation of small venules with endothelial destruction
- Subacute: well circumscribed necrosis/coagulation, stromal macrophage reaction around the necrosis and proliferative vasculopathy with narrowing of the lumen

- chronic : replacement of the parenchyma by scar tissue with stromal focal lymphocytic infiltration and subendothelial cell proliferation an or complete lumen obliteration

1.9 Histologic reaction of neoplastic tissue to radiosurgery

There is a plenty of debate in the literature about the histological changes of target lesion after radiosurgery. The issue is as complex yet not understood.

The most common acute reactions after RS for benign meningiomas are symptomatic oedema and radio-necrosis (Kollova et al., 2007, Kondziolka et al., 2008b, Santacroce et al., 2012).

The clinical manifestations depend from target volume and location (Santacroce et al., 2014).

Radiobiological effect of radiosurgery is based on direct cytotoxic effect after low dose radiation therapy (Santacroce et al., 2013). Furthermore intratumor microenvironment greatly influences the radiosensitivity of tumor cells and is closely related to the functional status of tumor microvasculature (Park et al., 2012). Available information from AVM radiosurgery and meningioma radiosurgery has shown that normal vessels rarely decrease in size or occlude after radiosurgery and therefore they conclude that the abnormal vessels of neoplasms or vascular malformations have a relative sensitivity to radiosurgery in comparison to normal surrounding vessels since no occurrence of perforator occlusion leading to an infarct has been identified (Kondziolka et al., 2007). On the other hand it must also be said that chance to produce a damage of normal capillary vessels is directly proportional to the dose increasing (Yamamoto et al., 1992). In a recent review of the literature (Park et al., 2012) an analysis of the studies published about vascular damage in tumors after stereotactic high dose hypofractionated radiation therapy and radiosurgery was performed. The authors indicate that the functional vascularity in human tumors remains unchanged or improves slightly during the early period of conventional fractionated radiotherapy with 1.5–2.0Gy daily doses but gradually diminishes during the latter part of treatment. By delivering radiation doses higher than 10Gy in a single fraction or 20–60Gy in limited numbers of fractions severe vascular damage leading to the deterioration of the intratumor microenvironment and indirect death of

tumor cells is observed. Of note experimental data about radiation induced vascular damage shows that high dose delivery in single session produces decrease of vascular volume and increase of vascular permeability. It is also observed that radiation induced changes in blood perfusion, functional intravascular volume, and vascular permeability are directly related to the functional integrity and activity of endothelial cells. The authors strictly distinguished between endothelial cells derived from normal and tumor tissue classifying them as radioresistant and radiosensitive, respectively, in accordance with other experimental lines of evidence (Grabham et al., 2011) demonstrating that developing vessels are more radiosensitive than mature vessels. Most specifically as reported by the authors (Park et al., 2012) the death of endothelial cells after direct radiation damage would cause focal microscopic or macroscopic vascular damage and collapse of the affected capillary-like vessels. Soon after vascular permeability in tumors increases rapidly after irradiation due to damage in the endothelial cells followed by widening of the gaps between endothelial cells. Further extravasation of plasma due to vascular permeability might increase the erythrocyte concentration within the narrow capillaries, thereby leading to retardation or stasis of blood perfusion. In addition, the increased permeability of capillaries may increase the extravascular or interstitial plasma protein concentrations, thereby elevating interstitial fluid pressure. The elevation of interstitial fluid pressure above the intravascular blood pressure will cause vascular collapse. Therefore, it is probable that the early decline in functional vascularity after irradiation in tumors may be caused at least in part by collapse of blood vessels as a result of elevation of interstitial fluid pressure. When tumor volume shrinks due to death of parenchymal cells after irradiation, the tumor vascular beds may become further disorganized, aggregated, and fragmented.

The authors concluded that the radiation-induced vascular damage and the resulting indirect death of tumor cells play important roles in the response of tumors to high dose hypofractionated radiotherapy and radiosurgery. In addition, enhanced immune reactions and

increased eradiation of cancer stem cells might be involved in the response of tumors to stereotactic fractionated radiotherapy and radiosurgery (Liu et al., 2013, Park et al., 2012).

A recent review of the literature (Park et al., 2012) about vascular damage in tumors after stereotactic high dose hypofractionated radiation therapy and radiosurgery indicate that the functional vascularity in human tumors remains unchanged or improves slightly during the early period of conventional fractionated radiotherapy with 1.5–2 Gy daily doses but gradually diminishes during the latter part of treatment. By delivering radiation doses higher than 10Gy in a single fraction or 20–60Gy in limited numbers of fractions severe vascular damage leading to the deterioration of the intratumor microenvironment and indirect death of tumor cells is observed. Of note experimental data about radiation induced vascular damage shows that high dose delivery in single session produces decrease of vascular volume and increase of vascular permeability. The death of endothelial cells after direct radiation damage would cause focal microscopic or macroscopic vascular damage and collapse of the affected capillary-like vessels. Soon after vascular permeability in tumors increases rapidly after irradiation due to damage in the endothelial cells followed by widening of the gaps between endothelial cells. The authors concluded that the radiation-induced vascular damage and the resulting indirect death of tumor cells play important roles in the response of tumors to high dose hypofractionated radiotherapy and radiosurgery. In addition, enhanced immune reactions and increased eradiation of cancer stem cells might be involved in the response of tumors to stereotactic fractionated radiotherapy and radiosurgery(Park et al., 2012).

1.10 Physical Considerations

The physical priniciples of radiosurgery are as for any other photon based radiation treatment based on the use of ionizing radiation delivered to a small target volume. Some definitions should be provided (Santacroce et al., 2014):

1.10.1 Radiation

Event described as energy sent out either as wave (photons) or as particle (protons heavier ions or electrons) in a given time and space. Radiation is classified in ionizing and not ionizing. Ionizing radiation is produced by artificial or natural radioactive nuclides, either particles or high energy electromagnetic waves with enough energy to produce an atomic ionization. The interaction produces changes either in the given matter or the given radiation too. The ionization of a given atom can be direct (protons heavier ions or electrons) or indirect (photons) (Santacroce et al., 2014).

1.10.2 Radioactivity

Radioactivity can be defined as capacity or property of an instable atomic nucleus of a given element to send out radiation getting to a more stable state. It can be described as emission might of α, β or γ rays, each of them has specific decay mode, capacity of interaction with matter with respect to energy, depth of distribution and biological efficacy (Santacroce et al., 2014).

1.10.3 Decay modes:

- α rays (i.e. double charged helium nuclei): densely ionizing radiation they are not applied in clinical radiotherapy because of to their short shield distance and high biological effect. (Santacroce et al., 2014)
- β rays: either positive and negative decay. They are weak ionizing rays. 60Co was the isotope which found clinical application for radiosurgery Gamma Knife based, its decay mode is shown in Fig. 6. (Santacroce et al., 2014)

- γ rays: electromagnetic radiation photons. No mass any charge. They produce indirect and weak atomic ionization. (Santacroce et al., 2014)

1.10.4 Interaction of ionizing radiation with matter

- Atomic particles: subatomic bodies with given mass, radium and sometimes charge. Protons, neutrons, heavier ions (carbon ions) and electrons (Santacroce et al., 2014).
- Photons: electromagnetic bundles-packets of energy without mass and any charge with given wave frequency ν and length λ emitted either as X rays or as γ rays (Santacroce et al., 2014).

1.10.5 Principles of dose planning and dosimetry in radiosurgery

The application of given dose is usually applied considering following variables (Santacroce et al., 2014) :

- Isodose line: curve within a planar point connecting the same dose (Santacroce et al., 2014).
- Isocentre: point in space through which the central beam of radiation passes ideally at center of the target (Santacroce et al., 2014).
- Depth dose distribution: dose distribution along the central radiation beam (Santacroce et al., 2014).
- Dose distribution: distribution of the energy dose in a given space delineated in Isodose curves (%)(Santacroce et al., 2014).
- Dose in line profile: dose distribution along a straight line (Santacroce et al., 2014).
- Dose cross line profile: dose distribution along a straight line perpendicular to central beam(Santacroce et al., 2014).

- Dose cross line distribution: dose distribution in the plan perpendicular to central beam (Santacroce et al., 2014).

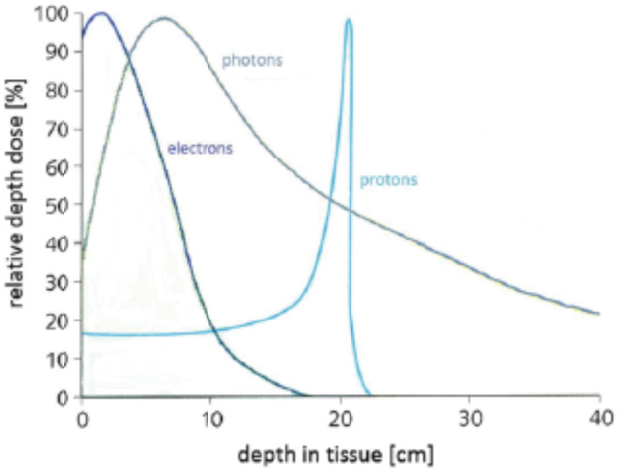


Fig. 3 Depth dose distribution of photons compared to electrons and protons
From A. Santacroce , M. A. Kamp, I. Simiantonakis , H. J. Steiger, W. Budach and J. Regis, "Treatment of Benign meningiomas Using Radiosurgery in "Imaging, Glioma and Glioblastoma, Stereotactic Radiotherapy, Spinal Cord Tumors, Meningioma, and Schwannomas " , Vol. 11 of Tumors of the Central Nervous System, M.A. Ed.; Springer Science + Business Media B.V., Dordrecht, 2014, pp 285-30 (With permission).

Transverse dose profiles are usually measured in the x (crossplane) or y (inplane) directions perpendicular to the radiation beam, and at a given depth (z) in the phantom. Dose measurements taken along the z direction create radiation dose distribution known as a depth-dose curve (Santacroce et al., 2014).

Radiation therapy can be applied with several machines (see following paragraph) by using photons with an energy spectrum between 1.2 and 25 MV and particles like protons and heavier ions like carbon ions. A comparison of the depth dose distribution between photons electrons and protons is shown in Fig. 3.

For radiosurgery in particular a single high dose of energy sent out by ionizing radiation is applied in all cases with photons either produced by a linear accelerator (linac) through emission of x rays emitted with Bremsstrahlung, using a photon energy applied of 6 MeV or

obtained by the decay of the radioactive isotope of cobalt 60Co whose decay mode provides two γ emitting photons with an energy of 1.25 MV (Fig. 4).” (Santacroce et al., 2014)

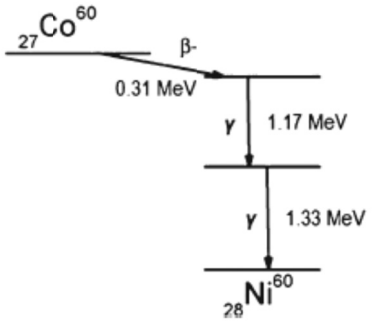


Fig. 4: Cascade decay of 60 Cobalt applied for the Gamma Knife radiosurgery system: β- decay ray changing inactive 60 Ni. Afterwards the active Nickel gets stabilized to 60 Nickel through emission of two photons γ ray emitting with an average energy of 1.25 MV
From A. Santacroce , M. A. Kamp, I. Simiantonakis , H. J. Steiger, W. Budach and J. Regis, “Treatment of Benign meningiomas Using Radiosurgery in "Imaging, Glioma and Glioblastoma, Stereotactic Radiotherapy, Spinal Cord Tumors, Meningioma, and Schwannomas " , Vol. 11 of Tumors of the Central Nervous System, M.A. Ed.; Springer Science + Business Media B.V., Dordrecht, 2014, pp 285-303 (With permission).

1.11 Principles of dose planning

1.11.1 conventional dose fractionated radiotherapy

The clinical practice of radiation therapy requires both appropriate clinical skills technical expertise (Barrett et al., 2009)

The landmark guidelines of the International Commission on Radiation Units (ICRU) Report 50 (1993), 62(1999) and 71 (2001) provide a description of target volumes in classical dose fractionated radiotherapy (Barrett et al., 2009)(Monti et al., 1995, Bourland, 1995, Denham et al., 1994) (Muren et al., 2005, Stroom and Heijmen, 2002, Chavaudra and Bridier, 2001, Berthelsen et al., 2007**)** (Fig. 5):

- **Gross Tumor Volume (GTV)** Volume with the surgical or diagnostic secured tumor tissue (Barrett et al., 2009)

- **Clinical Target Volume (CTV)** GTV with a safety margin including typical tumor spread area (infiltration zone + LN metastases) and a potential tumor spread area (distant Lymphnodes, cavities, subarachnoid Liquor spaces) (Barrett et al., 2009) .
- **Planning Target Volume (PTV)** CTV with safety margin including potential change in position of the tumor, mobility of the organs, weight change of the patient and positioning and storage uncertainties of the patient (Barrett et al., 2009).

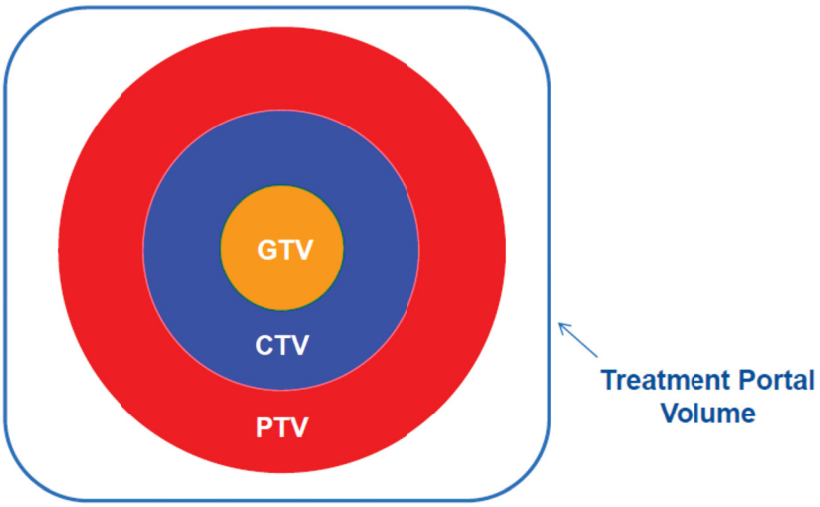


Fig. 5 schematic representation of "target volumes" in dose fractionated radiation therapy: GTV – gross tumor volume CTV clinical target volume PTV planning target volume. The treatment portal volume includes the tumor volume, potential areas of local and regional microscopic disease around the tumor, and a margin of surrounding normal tissue. Modified from Barrett, A., Dobbs, J., Morris, S. & Roques, T.. 2009. Principles of radiotherapy planning , in practical radiotherapy Planning fourth edition CRC Press Taylor & Francis Group (With Permission).

- **Gross Tumor Volume**

This classification is based on concepts in general oncology. According to the ICRU Report 50 GTV is the primary tumour or other tumour mass known shown by clinical examination or by imaging. Out of CNS GTV is classified by staging systems like TNM Classification for malignant tumours. Tumour volume location and shape may appear to vary depending on the imaging techniques used. Classically GTV consists of primary tumor (GTV-T) and /or metastatic lymphoadenopathy (GTV/N) or distant metastases (GTV-M) (Barrett et al., 2009).

Concerning CNS GTV always contains the highest tumor cell density and is absent after complete surgical resection.

- **Clinical Target volume**

Clinical target volume (CTV) defines the GTV when present with subclinical microscopic disease. The CTV derives from biological characteristics of the tumor, local recurrence patterns and experience of the radiation oncologist. Among all volumes the CTV has the greatest geometrical uncertainity in the contouring of target volume (Barrett et al., 2009).

- **Planning Target volume**

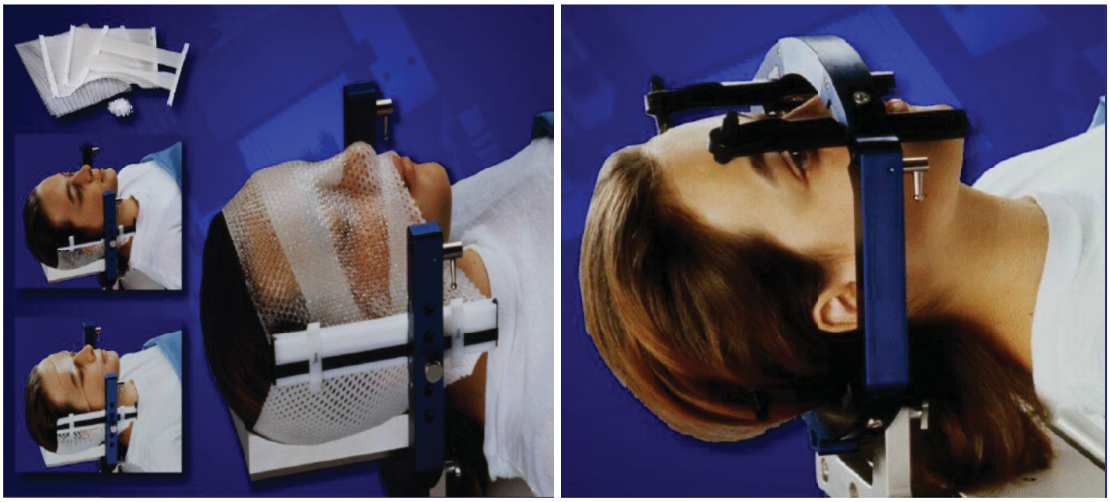
Further variable to consider in volume shaping is the possible patients organs movement during a fraction of treatment or between fractions (intra- or interfractionally). Therefore in order to ensure a homogeneous dose to the CTV over a dose fractionated schedules of irradiation, a margin should be added around the CTV. These take in consideration physiological organ motion and variations in patients positioning and alignment of treatment beams (set-up margin), creating a geometric reproducible planning target volume for daily dose fractionation. The planning target volume (PTV) is used in treatment planning to select irradiation beams to ensure that the prescribed target dose is actually delivered to the CTV (Barrett et al., 2009).

1.11.2 Stereotactic fractionated Radiotherapy and Radiosurgery

When radiation therapy is applied with support of a stereotactic system the goal of radiation therapy is not only the delivery of photon radiation to a target but also a high dose conformity accomplished with both stereotactic frames or maskes. In other words the radiation applied is the same but target volume concepts are massively different(Santacroce et al., 2013)(Santacroce et al., 2014).

As we have already detailed there is no biological advantage in dose fractionation with respect of imaging tumour control. Rationale of a dose fractionation is to lessen the dose to surrounding tissue. This can be achieved by using stereotactic frame based or frameless systems. There a number of stereotactic systems available. A detailed description of each system available is beyond the aim of this dissertation.

Basically a frame based system allows only a single session radiation whether a frameless system allows also a dose fractionated stereotactic treatment. Therefore the adjective "stereotactic" does not imply a single session treatment but only a support of system of coordinates which allows a highly conformal dose delivery (Fig 6).



a **b**

Fig. 6 a) Stereotactic mask and b) stereotactic frame for dose fractionated and Radiosurgery (Courtesy of Dr. R. Wurm Department of Radiation Oncology Klinikum Frankfurt Oder Germany and Mrs K. Racsai Brainlab Ag Munich Germany (copyright and trademark of Brainlab AG Munich, Germany)

Said this it is implicit that the target volume definition of a stereotactic treatment differs from a conventional one due to the conformity required. This brings to a deviation from the definition of volumes as defined in the over mentioned ICRU reports as follows (Fig. 7):

- Frameless Radiosurgery and/or dose fractionated radiotherapy

  GTV: Target volume

  PTV: Planning target volume (Usually GTV +1mm)

- Frame-based Radiosurgery

  TV: Target volume

  PIV: Planning Isodose volume (no setup Margin)

a b

Fig.7 (a) schematic representation of "target volumes" in stereotactic frameless dose fractionated radiation therapy: in Order to achieve better conformity there is no CTV and a setup Margin of 1mm PTV is defined (b) schematic representation of "target volumes" in stereotactic frame-based single session radiation therapy: in Order to achieve better conformity and selectivity there is no CTV and no further margin is required: TV: Target volume PIV: Planning Isodose volume

In order to achieve high dose conformality and selectivity some requirements are mandatory (Flickinger and Niranjan 2008):

- **Small target volume**: Reducing the volume of normal and target tissue irradiated improves tolerance
- **Sharply defined target**: Can be treated with little or no extra margin of surrounding normal tissue an or without unintentional under dosage of the target (marginal miss)
- **Sensitive structures excluded from target:** Reduces the treatment volume to match the target volume
- **High conformity**: Reduces the treatment volume to match the target volume
- **Accurate radiation delivery**: No margin of normal tissue needed for set up error and reduced chance of under-dosing target

1.12 Radiosurgery Devices

The first clinical application of radiosurgery was treating intracranial vascular lesions like AVM's. In the meantime it was applied also to benign tumours like vestibular schwannomas or meningiomas. Nowadays the spectrum of clinical indication of radiosurgery is spreading to the most various clinical diseases including brain metastases.(Santacroce et al., 2013)

Dose planning and volume targeting are essential issues of radiosurgery for meningiomas thus implying the use of adequate imaging diagnostic tool. (Santacroce et. al., 2014)

MRI imaging offers high quality target definition due to better enhancement of the target, less bone artefacts and, by using CISS sequences, better depiction of cranial nerves (Spiegelmann et al. 2010). On the other hand CT scan offers better appreciation of surrounding bone spaces and tissue photon attenuation (Elia et al., 2007). Although some authors recommend fusion of MRI and CT imaging just for small meningiomas using CT based plans for larger meningiomas, we recommend the use of both imaging diagnostic technique to perform radiosurgery for all meningioma cases regardless the volume.

A variety of devices are now available for commercial use to perform radiosurgery for benign meningiomas which is nowadays provided using two basic techniques of convergent beam technology:

1) Stereotactic 60Co based system "Gamma Knife"

2) Linear accelerator also called linac

3) modified linac based systems "Cyber knife"

Hereby follow the main features of each device available for radiosurgery (Santacroce et al., 2014). A detailed description of physics and technology is beyond the aim of this doctoral thesis. Nevertheless some details have to be clarified

1.12.1 Gamma Knife

The “Gamma Knife” uses variable number of multiple fixed converging Co60 sources (usually 192 to 201) constantly releasing two photons with an average energy of 1.25 MeV for each spontaneous decay aimed to a centre point(Elia et al., 2007). It is based on three structural concepts (Fig. 8):

- A spherical source bounding
- collimation helmets
- couch with electronic control

The radiation sources are on the surface of a hemispherical shaped shell each aimed at a single isocenter 40 cm from each source called Unit Centre Point. The UCP isocenter is targeted by using a stereotactic coordinate frame (Purdy, 2008, Santacroce et. al, 2014). The beams produced by these sources are then secondary collimated with collimation helmets of variable diameters (4, 8, 14 and 18 mm). It is possible to close each single of these beams by plugging the collimator allowing the individual beam patterns.

The constant decay of the cobalt sources implies a daily dose rate which at installation is set by ca 3-4 Gy/min with a half-life of approximately 5.3-6 years and thus with a replacement necessary every 7 years. 60Co isotopes have a relatively low energy (1.25 MeV) (Santacroce et. al, 2014).

Most plans have an isodose normalisation line of 50 % due to the source size and the steepest dose falloff in cross line dose profile of 60Co (Fig. 9). The total time to irradiate a single isocenter is of a few minutes thus making multiple isocenter plans practical. Since early 1980s many Gamma Knife models have been developed. From the prototype the model U to the model B providing arrangement of the sources on annular section of a hemisphere (Santacroce et. al, 2014).

Later model C and 4C were introduced with robotic positioning of treatment coordinates and with the last Model PERFEXION the collimation helmets were internally mounted and with different diameters (4, 8, 16 mm). Furthermore a major aperture allows also treatment of the cervical spine (Flickinger and Niranjan 2008) (Santacroce et. al, 2014).

The cobalt based Gamma Knife has in comparison to linear accelerators several advantages:

1) Constant beam/source pattern
2) predictable decay by well-known half-life, no daily output fluctuations.

Disadvantages are:

1) Reloading of the after complete source decay
2) Variable dose rate due to source decay
3) Application of normalisation isodose line of usually 50 % required due to its dose cross line profile of 60Co isotope producing a dose inhomogeneity between periphery and central point of the target volume

Recently a new frameless Gamma Device, “Gamma Knife Icon” has been introduced in Marseille in November 2015. The key advantage of the Icon device is the Combination of a frameless and frame based technology with multiple isocentric collimation dose plans; furthermore it is capable to perform both radiosurgery and stereotactic dose fractionated radiation therapy.

Fig. 8: Gamma Knife Perfexion (copyright and trademark of ELETA Instruments AB Stockholm Sweden) Courtesy of Dr Anne-Charlotte Särnman | Client Marketing Manager Region Europe AFLAME Elekta Instrument AB.

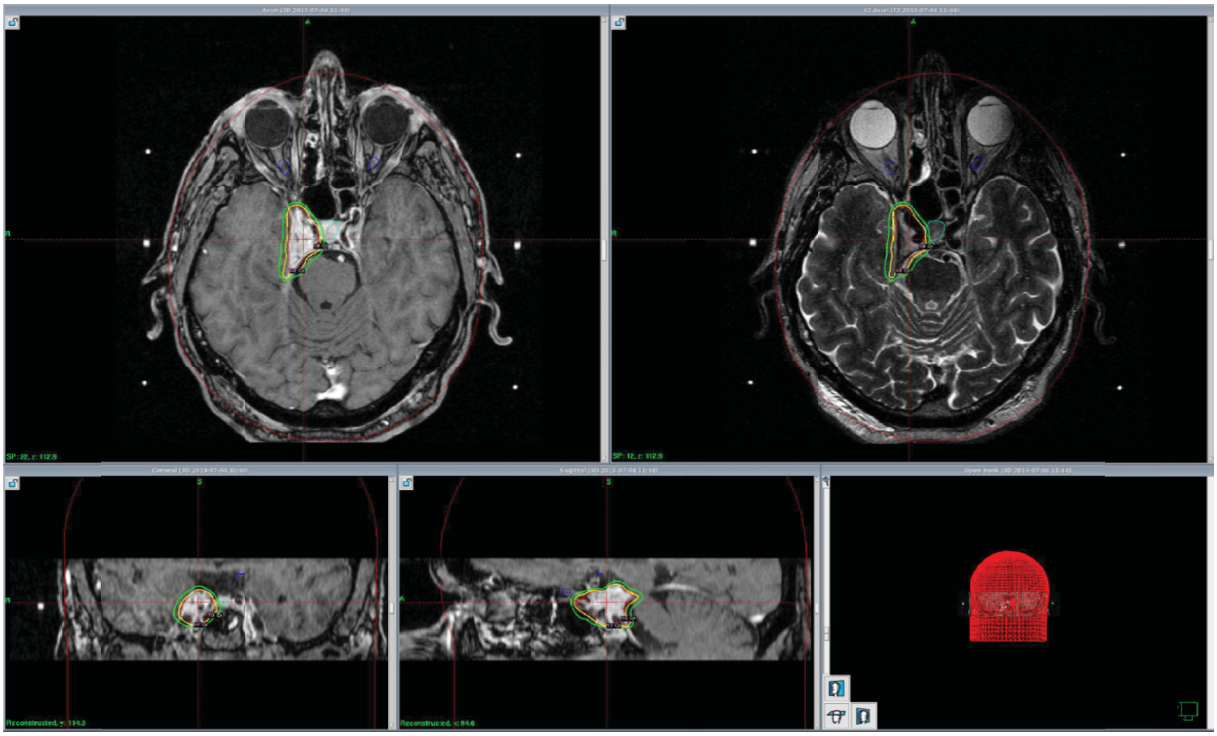


Fig.9: Dose Plan of a right cavernous sinus meningioma Leksell Gamma Plan (copyright and trademark of ELETA Instruments AB Stockholm Sweden) Courtesy of Dr ATCJ van Eck MD Gamma Knife Zentrum Krefeld, Germany

1.12.2 **Linear Accelerators** (Santacroce et al., 2014)

As we have already detailed a linear accelerator (also called linac) is the most widely and common machine used to conventional radiotherapy (Fig 10).

The physical principle at the basis of linac radiation is the Bremsstrahlung: ionizing radiation of a given volume produced by the collision of accelerated electrons as microwaves properly amplified with a metal target which, when in photon mode, emits X-rays that are properly collimated to irradiate the target.(Santacroce et al., 2014)

Conversely to a Gamma Knife invented as a dedicated radiosurgery device, LINAC devices are usually developed for conventional dose fractionated Radiotherapy; only some dedicated linacs may perform radiosurgery or stereotactic fractionated radiotherapy incorporating stereotactic guiding devices to guarantee better conformity and dose falloff.

Moreover, apart from the physical principle of the Bremsstrahlung the dose planning is not based on multiple isocentric conic collimators but on multiple non coplanar radiation arcs converging. Radiating arcs are produced by rotation of the gantry and couch angle dynamic arc and it is produced by simultaneous rotation of gantry and couch with a “rapid dynamic arc” technique(Santacroce et. al, 2014).

Key difference of linac based radiosurgery is that the dose pattern of conic collimators is not adequate to a single isocenter radiation source where a spherical dose is created. The latest stereotactic linac devices are equipped with tertiary micro multileaf collimators, achieving highly conformal and homogeneous dose distributions obtained by the application of an isodose normalisation line of 80 % delivering radiation to a single isocentre(Santacroce et. al, 2014).

The introduction of micro-multilieaf collimators has deeply transformed the practice of linac radiosurgery. Thorough the use of single isocentre planning and radiation delivery there is a more homogeneous radiation distribution across the target, basically not achievable with

multiple isocentres planning. Nevertheless this dosimetric difference, according to clinical data, seems to be not clinically relevant given that inhomogeneity dose distribution within the target does not interfere with the main goal of the treatment which is to control/eliminate the tumour (Spiegelmann et al., 2010, Spiegelmann et al., 2002).

Currently many devices are used to perform linac based radiosurgery: X Knife (Radion Inc. Burlington MA U.S.A) Novalis (Brainlab Heimstetten Germany) etc. (Santacroce et al. 2014)

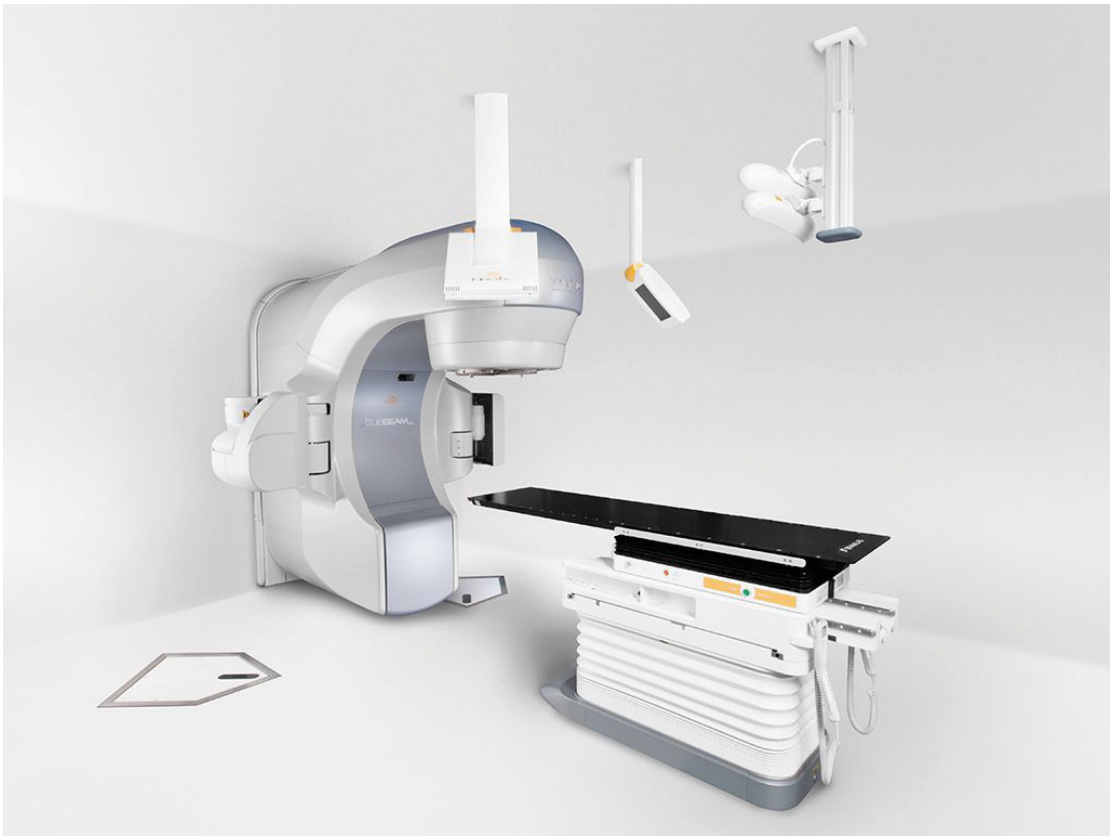


Fig. 10: Varian Truebeam STx Linac with Brainlab Exactrac equipment for stereotactic radiation therapy Courtesy of Mrs K Racsai Brainlab AG Munich German (copyright and trademark of Brainlab AG Munich, Germany)

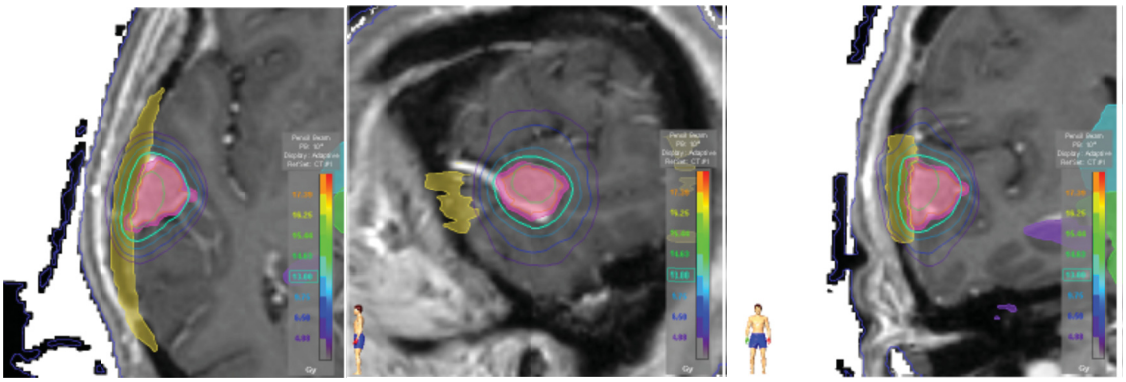


Fig. 11: Dose Plan of a right temporal basal meningioma with I Plan (copyright and trademark of Brainlab AG Munich, Germany) Courtesy of Dr H. Gottschlag PhD Department of Radiotherapy and Radiation Oncology Heinrich Heine University Düsseldorf Germany

1.12.3 Cyber Knife

The Cyber Knife (Accuray Inc. Sunnyvale CA U.S.A) (Fig. 12) combines the technology of a miniaturized linac on a robotic arm with a system for target tracking and beam realignment. It emits 6 MV photons with single conic collimator. The physical radiation process is as for a linac the bremsstrahlung . Contrary to the latest linac devices Cyber Knife has no multileaf collimators. Radiation dose planning is achieved due to multiple fixed beams and isocenters . Stereotactic coordinates are defined without frame(Santacroce et. al, 2014).

Target position is verified during radiation by using to X-rays diagnostic cameras and an optical tracking system constantly proving the patients/target's position. This system is provided also by other linac radiosurgery systems. This feature should not be confused with an image guided radiotherapy technique (IGRT), which provides the combination of a three dimensional imaging with conformal treatment delivery. This is accomplished by the addition of CT imaging capability to a linac unit with stereotactic equipment(Santacroce et. al, 2014).

Advantage is freedom of movement in the space of the robotic arm to deliver radiation compared to classical linac (Fig. 13) (Santacroce et. al, 2014).

Disadvantage is the technology of the miniaturized linac which makes the total treatment time relatively long and the application of a mask to for treatment time might be uncomfortable for the patient.(Santacroce et al. 2014)

A growimg number of reports shows good clinical rsutls in the short to medium term Follow Up for the management of intracrnanial meningiomas, WHO Gr. II and Gr. III in particular (Galkin et al., 2015, Romanelli et al., 2007, Zhang et al., 2016).

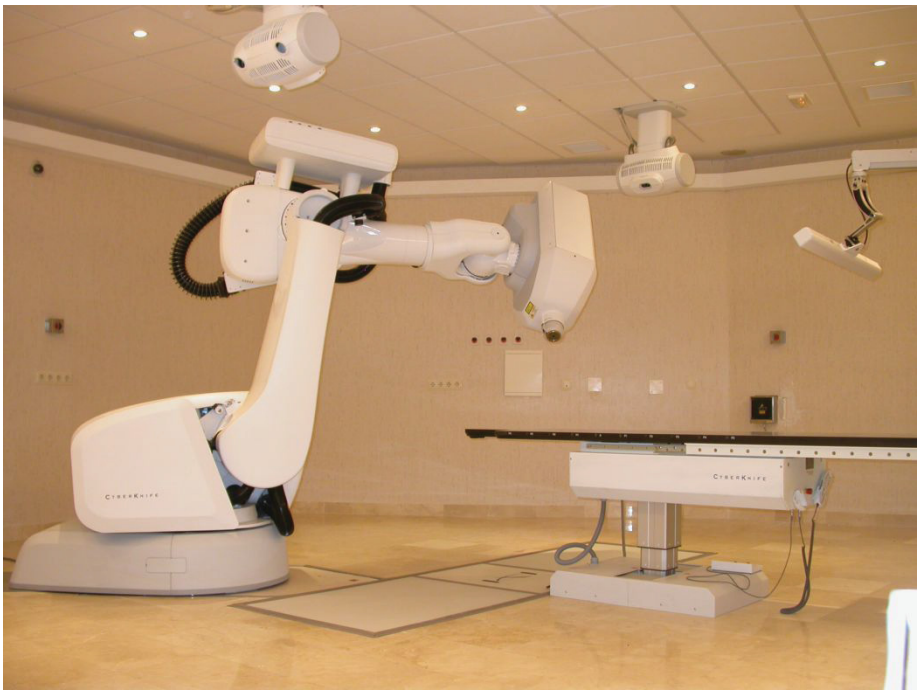


Fig. 12: Cyber Knife System (copyright and trademark of Accuray Inc. Sunnyvale CA U.S.A) : dedicated linac device equipped with a robotic arm (Courtesy of Dr. Roberto Martinez Alvarez, MD PhD Department of Functional Neurosurgery, Hospital Ruber Internacional, Madrid, Spain)

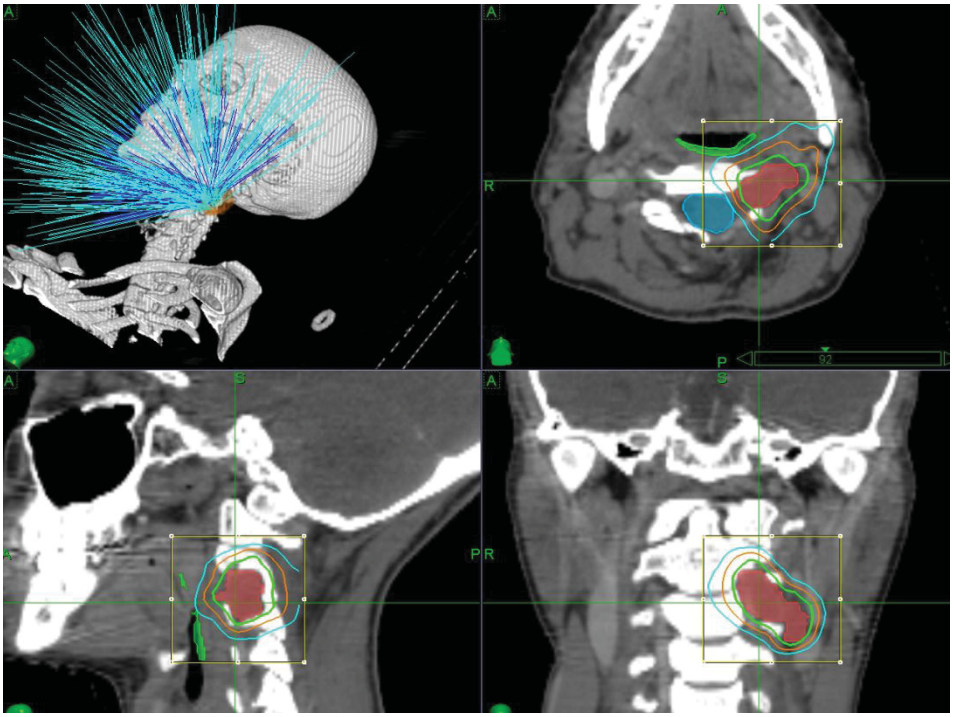


Fig. 13: Doseplan of C2 Schwannoma with the Cyber Knife System (copyright and trademark of Accuray Inc. Sunnyvale CA U.S.A): (Courtesy of Dr. Roberto Martinez Alvarez, MD PhD Department of Functional Neurosurgery, Hospital Ruber Internacional, Madrid, Spain)

2 Aim of the doctoral thesis

This doctoral thesis is based on a multicentre retrospective observational study about long term outcome of GK radiosurgery for benign intracranial meningiomas.

The Ethic Commission of the Medical Faculty of the Heinrich Heine University of Düsseldorf approved this study (Study Number 4002).

The introduction provides a description concerning definition biology and physics of radiosurgery. Technical description of the machines nowadays available and about physics of radiosurgery is presented according to a book chapter published by the candidate (Santacroce et al., 2014) A review of the radiobiological principles of radiosurgery is key point of the introduction and refers to a recent review of the literature published by the candidate (Santacroce et al., 2013) .

A multicenter retrospective study about radiosurgery for intracranial meningiomas is performed on behalf of the European Gamma Knife Society under supervision of the participating European centres.

First aim of the study is to assess tumor control rates after RS and to evaluate the variables influencing the imaging tumor outcome. Second endpoint is to confirm treatment safety after by establishing neurological improvement rates and complication rates after RS.

The original paper provides a discussion about any variable influencing the imaging outcome and comments about the safety of the procedure. Starting from that the thesis provides a more detailed discussion with comments from the most recent contributions of the literature and further results of sub group analyses performed after publication of the main sample.

3 Published original research

Santacroce A, Walier M, Régis J, Liščák R, Motti E, Lindquist C, Kemeny A, Kitz K, Lippitz B, Martínez Álvarez R, Pedersen PH, Yomo S, Lupidi F, Dominikus K, Blackburn P, Mindermann T, Bundschuh O, van Eck AT, Fimmers R, Horstmann GA.
Long-term tumor control of benign intracranial meningiomas after radiosurgery in a series of 4565 patients.
Neurosurgery. 2012 Jan;70(1):32-9; discussion 39. doi: 10.1227/NEU.0b013e31822d408a.
PMID:21765282

4 Discussion

This dissertation is based on an original paper about long term follow up of benign intracranial meningioma as after GK radiosurgery. The analysis of PFS rate showed surprisingly that many variables may influence imaging outcome stratifying the sample analysis per intracranial location, gender, and number of meningiomas treated. Each of these points is discussed in detail in the discussion of the manuscript (Santacroce et al., 2012).

Nevertheless since the manuscript has been published four years ago already further contributions have provided more inputs about this issue and thus deserving a further comment (Santacroce et al., 2014)

Recently The North American Gamma Knife Consortium published several landmark contributions about radiosurgery for skull base meningiomas (Starke et al., 2014, Ding et al., 2014, Sheehan et al., 2015b, Sheehan et al., 2014). Each of them details about variables influencing imaging and neurological outcome underlying remarkable differences when performing radiosurgery that should be taken into consideration(Rogers et al., 2015).

4.1 Imaging tumor control

It is well known that the main achievement in radiosurgery remains imaging control of the irradiated target volume defined as stable or shrinking without occurring of new clinical symptoms and/or worsening of the patient's neurological picture(Santacroce et al., 2012).

The main achievement of microsurgery is complete tumor removal with dural tail and when necessary neighbouring bone (Santacroce et al., 2012).

According to these results the indication to radiosurgery should be cautiously be given according to prior surgical manipulation, patients' gender, intracranial location and number of lesions treatment per patients or possible syndromic pictures (Santacroce et al., 2012).

4.1.1 The issue “histology”

There is a big debate about the necessity of histological confirmation of an imaging defined tumor lying in deep sitting intracranial location. Interestingly a prior histological confirmation, contrary to other series (Kollova et al., 2007), seems to negatively influence imaging tumour outcome after radiosurgery (Santacroce et al., 2012). This finding has been confirmed by other more recent reports. Pollock et al. reported on 188 patients with benign or presumed benign meningiomas treated using either surgery or RS alone. With a median follow-up of 64 months, 7-year PFS with RS and Simpson Grade 1 surgery were equivalent (95% and 96%, respectively). However, RS resulted in better tumor control when compared with cyto-reductive surgery. The authors concluded that RS should be a primary option when Simpson Grade 1 resection cannot be achieved(Pollock et al., 2003). These results were confirmed in updated analysis of Radiosurgery in definitive setting(Pollock et al., 2012b).

4.1.2 The issue “target dose”

Further major issue is the dose necessary to achieve imaging tumor control. According to the latest contributions available in the literature (Kondziolka et al., 2008b, Santacroce et al., 2012) increasing dose delivered to the margin may not influence imaging tumor control. For benign intracranial meningiomaa, excellent local control has consistently been achieved with 12 to 16 Gy.

Ganz and colleagues noted that treatment with a target margin dose of 10 Gy or less was associated with higher recurrence rate risk, compared with a dose of 12 Gy or higher .32 Other reports suggest that low dose application to the margin, below to 12 Gy at median isodose line of 50 %, is associated to an increased rate of tumor enlargement (Elia et al., 2007, Kollova et al., 2007).

Stafford et al. reported no reduction in local control at 5 years with tumor margin doses of less than 16 Gy as compared with doses greater than or equal to 16 Gy (Stafford et al., 2001).

Kondziolka et al. reported no better imaging outcome with marginal doses greater than 15 Gy versus less than 15 Gy (Kondziolka et al., 2008b).

It is still unclear whether target dose, either at the margin or at the maximum point of the target might influence imaging outcome; a subgroup analysis of the sample published focused on 468 pure petroclival meningiomas showed statistical relevance with respect of target margin dose toward imaging tumor control rate in both univariate and multivariate analyses ($p< 0.0001$). This finding has been also reported in a multicentric review of 763 patientes treated with RS for sellar and parasellar meningiomas: a target dose lower than 13 Gy was associated to worse imaging outcome ($p<0.001$)(Sheehan et al., 2014). A further report about RS for petroclival meningiomas of the North American Gamma Knife Consortium confirmed the statistical relevance of both margin and maximal dose at the target. The definition of target dose is historically based in gamma knife radiosurgery on delivery of margin dose at the target's periphery applied to a given isodose line (usually 50% for cobalt baesd devices) and and maximum dose at the centre of the target through multiple isocentric round collimators. As previously reported lower control rates are noted at lower prescription doses (Pollock et al., 2012a, Pollock et al., 2012b, Kollova et al., 2007, Kondziolka et al., 2008b, Kondziolka et al., 2007). This might have a radiobiological background. A raw estimation of the normalized tissue dose (biological effective dose) of 12 Gy applied in single-fraction, is approximately 42 applied in 1.8/2 Gy daily fraction size of conformal dose fractionated radiotherapy EBRT, assuming an α/β ratio of two and a 2-Gy fraction size for benign meningiomas.

Currently fractionation dose schedules for WHO Grade I meningiomas range typically from 50 to 55 Gy with a daily of 1.8 to 2.0 Gy(Elia et al., 2007, Pollock et al., 2012a).

As a result, single-fraction radiation doses below 13–14 Gy may be too low, and might bring poorer imaging outcome (Santacroce et al., 2012).

4.1.3 The issue “target volume”

Target volume is a factor predicting poorer imaging tumour control (48). DiBiase and colleagues reported a 92% 5-year disease-free survival for patients with meningiomas smaller than 10 cm^3 as opposed to 68% for larger tumors (DiBiase et al., 2004, Rogers et al., 2015). Kondziolka reported excellent outcomes with RS for meningiomas till a major diameter of 3.0 cm or a target volume of 7.5 cm^3 (Kondziolka et al., 1998). Other authors have found excellent local control and fewer radiation-related complications with smaller meningiomas, with complications rate ranging from 4.8% with tumors in the volume smaller than 3.2 cm^3 but in 22.6% for larger volumes (> 9.6 cm^3)(Pollock et al., 2012a, Pollock et al., 2012b, Rogers et al., 2015). This is also confirmed by more recent clinical reports (Elia et al., 2007, Pollock and Stafford, 2005, Kondziolka et al., 2008b, Rogers et al., 2015). A further sub group analysis of 254 petroclival meningiomas treated with radiosurgery reported a favorable imaging outcome for smaller tumors (p=0.003) (Starke et al., 2014). This finding was also reported in a sub group analysis RS for parasagittal and parafalcine meningiomas (post RS edema p=0.040)(Sheehan et al., 2015a) but was not significant predictor for RS of cerebello pontine angle meningiomas (p=0.07) (Ding et al., 2014). To conclude a large analysis of RS of 675 patients hoarourgin meningiomas of the posterior cranial fossa (PCF) showed that increasing tumor volume was associated to worse imaging outcome (p=0.005) (Sheehan et al., 2015b)

4.1.4 The issue “gender”

Poorer control in male than female patients has been previously reported (Rogers et al., 2005, DiBiase et al., 2004, Santacroce et al., 2012). The reason for that remains nowadays still unclear. A hormonal setting has been postulated as being a possible factor (Sanson and Cornu, 2000). This hypothesis has been confirmed by more recent evidences, in particular with

regard to progesterone (Ohla and Scheiwe, 2015, Sheehy and Crockard, 1983, Santoro et al., 1999).

In the analyzed cohort gender shows to be highly significant factor towards imaging tumor outcome in both univariate and multivariate test setting (Santacroce et al., 2012). This finding has been recently been confirmed by other reports. Starke and others after analyzing the variables influencing imaging and clinical outcome after RS for petroclival meningiomas found that male gender was predictive of worse imaging outcome (Starke et al., 2014).

4.1.5 The issue "multiple meningiomas and syndromic pictures"

We have already detailed that patients harboring more than one meningioma show poor imaging outcome compared to those harboring one meningioma (Santacroce et al., 2012).

There are very few data about the management of multiple meningiomas. Some points need to be cleared: there is no consensus about the definition of "multiple meningiomas". In our database we defined patients with multiple meningiomas every patient harboring at least two meningiomas and in case of previous microsurgical resection not recurring from the same surgical field (tumor bed). This definition is confirmed in a recent case report defining multiple meningioma as at least two spatially separated meningiomas occurring simultaneously or more than two meningiomas arising sequentially from two clearly distinct regions(Ohla and Scheiwe, 2015, Spallone et al., 1999). To make the issue more complicated there is no clear criterion of distinction between patients with multiple meningiomas and syndromic pictures like frank meningiomatosis and neurofibromatosis. Ohla reports that since multiple meningiomas can be associated with other neoplasms such as neurofibromatosis, the distinction between true multiple meningiomas and those which should be considered as a special variant of von Recklinghausen's disease is not always clear‐cut. Furthermore several case reports on familial meningiomatosis in patients without neurofibromatosis have been published prior to the National Consensus Statement on Neurofibromatosis in 1987, which

would nowadays be considered to have neurofibromatosis (Atkinson and Lane, 1994, 1988b, 1988a, Ohla and Scheiwe, 2015).

An Estimation of the prevalence of meningiomatosis unrelated to NF2 might be therefore nevertheless rare very difficult (Maxwell et al., 1998, Ohla and Scheiwe, 2015). Confluent meningiomas or clusters of meningiomas are referred to as diffuse meningiomatosis, which is considered to be an extreme form of multiple meningioma (Ohla and Scheiwe, 2015)

Radiosurgery of this peculiar samples are associated with a worse imaging outcome (Rogers et al., 2015). Our sub analysis shows how PFS rate for patients receiving RS for more than meningiomas or with a frank syndromical diagnosis tend to show poorer imaging outcome. It has to be said that patients with clear neurofibromatosis tend to show comparable imaging control rates to patients with multiple meningiomas and meningiomatosis A Recent contribution of the literature

Although multiple meningiomas are reported frequently a diagnosis of pure meningiomatosis restricted to one cerebral hemisphere is very rare. Complete resection with clear surgical margins to avoid recurrence should be the treatment of choice. In any case of incomplete resection or upon recurrence or in case of step by step resection adjuvant stereotactic radiotherapy might be an option. (Ohla and Scheiwe, 2015).

For sure a patterns of genetic mutations have been observed in syndromic multiple meningiomas picture: loss of the same Chromosome 22 or inactivation of the same X Chromosome seem to be determining factors (Lomas et al., 2002, Zhu et al., 1999). There are many theories about the patho-physiological mechanisms of spreading of multiple meningioma. Some authors suggest spreading through the arachnoidea and the cerebro-spinal fluid. Other tend to emphasize the role of the over mentioned mutations patters and tend to believe that multiple meningiomas arise from a single clone cell (Lomas et al., 2002, Zhu et al., 1999, Ohla and Scheiwe, 2015, Petrella et al., 1993).

There are not clear guidelines for the management of this challenging pathological condition

The decision should be taken in interdisciplinary setting. The role of radiation therapy is so far unclear but seems to be effective treatment option. More intriguing is whether a stereotactic fractionated radiation therapy were bigger radiation fields are possible might have better imaging outcome over radiosurgery given the chance of including larger safety margins and to reducing the rate of out of filed recurrences.

Our cohort shows a quite predictable worse imaging outcome for both samples with multiple meningiomas clear NF2 if compared to sporadic meningiomas. Interestingly no difference was observed with respect to imaging control rate in those subgropus (Santacroce et al., 2012). More recently Liu and coworkers reported about a small series of 12 patients harbourign 125 meningiomas with NF2. 87 meningiomas were symptomatic or progressive and underwent RS. 5 years local tumor control rate was 92%. Distant treatment failure rate was 77%. Median Follow Up range was 43 months. Influencing variables predictive for distant failure were male gender ($p=0.036$) ,age at distant failure ($p<0.0001$) and prior number of RS treatments ($p=0.0049$)(Liu et al., 2015)

4.1.6 The issue "Tumor location"

Tumor location is a predictive variable influencing imaging tumor control (Santacroce et al., 2012). The European gamma knife society experience (Santacroce et al., 2012) together with other reports (Kondziolka et al., 1998, Kollova et al., 2007, Santacroce et al., 2012, Pollock et al., 2012b) confirmed worse imaging outcome for located in parasagittal region, falx, or convexity compared to skull-base tumours.(Santacroce et al., 2014).

Unlike the difference in imaging control rates among patients' gender and among tumors with and without previous microsurgical manipulation, the reason for worse imaging tumor control for tumors located in parasagittal, falx, or convexity is not understood yet **(**Santacroce et al., 2014).

It has been postulated that meningiomas in these location have vascular pattern of supplying a pial vessel without proper cerebrospinal cisternal draining apparatus (Kollova et al., 2007). This factor together with frequently larger target volume and larger brain parenchyma/tissue irradiated and then the margin faces of brain tissue in contact with cerebrospinal may increase the incidence rate of symptomatic edema and imaging failure (Santacroce et al., 2014)

It is possible that different histologic subtypes of benign meningiomas are more radiosensitive than others, but further study is needed to examine this variable as a predictor of imaging control success after Radiosurgery (Perry et al., 1997b, Perry et al., 1997a).

4.2 Clinical outcome and Toxicity of radiosurgery

A number of clinical reports show that that RS is safe method for managing benign intracranial meningiomas, (Santacroce et al., 2012, Kondziolka et al., 2008b, Condra et al., 1997, Kollova et al., 2007, Liscak et al., 2004, Sheehan et al., 2014, Kondziolka et al., 2008a, Kondziolka et al., 2003, Flickinger et al., 2003, Lee et al., 2002, DiBiase et al., 2004, Pollock et al., 2012a, Pollock et al., 2012b, Pollock and Stafford, 2005, Stafford et al., 2003, Pollock et al., 2003, Pollock, 2003, Stafford et al., 2001). In our experience, while not statistically verified the permanent morbidity rate of 6.6 % confirms the data reported in literature (Santacroce et al., 2012)(Santacroce et al., 2014).

More recent contributions (Pollock et al., 2012a, Pollock et al., 2012b) show a permanent complication rate of 11 % with more than one-half related to cranial nerve dysfunction. A difference between this series and other recent reports is the radiation dose the median tumor margin dose over the entire study period was 16 Gy. This dose concept is higher if compared to other reports like Prague (median, 12.6 Gy) (Kollova et al., 2007) Pittsburgh (mean, 14 Gy) (Kondziolka et al., 2008b) and the European gamma Knife Society(median, 14 Gy) (Santacroce et al., 2012).

The variety of side effects that may arise after radiosurgery is related to many factors: tumor location, tumor volume and shape, dose delivered, eloquence of the neuro-vascular structures close to the target volume: symptomatic edema and consequent tumor/brain swelling and cranial nerves dysfunctions are the most frequent; rare are episodes of vascular occlusion with an incidence of 1–2 %; delayed hydrocephalus is also reported (Elia et al., 2007, Barami et al., 2007, Bloch et al., 2012)(Santacroce et al., 2014)

Several reports indicate in both univariate and multivariate analysis setting that patients with tumors of the parasagittal/falx/convexity regions tend to show three times higher chance to develop permanent complications compared to patients with tumors involving the skull-base or tentorium(Pollock et al., 2012a, Pollock et al., 2012b, Kollova et al., 2007).

Increasing target volume is also a risk factor. Kollova et al. noted that the 5-year risk of post-radiation edema was 30 % for patients with benign meningiomas larger than 10 cc compared to 10 % for patients with target volumes smaller than 5 cc (Kollova et al., 2007).

In the recent series from Kondziolka only increasing target volume was significant factor associated with treatment related complications (Kondziolka et al., 2008a).

The prescription dose is another variable influencing the incidence of complications. The radiosurgery group from Prague performed a detailed analysis to determine the optimal radiation dose for benign meningioma radiosurgery. They report that patients receiving a tumor margin dose lower than 12 Gy had a higher chance of imaging tumor progression, while patients receiving a tumor margin dose higher than 16 Gy had an increased risk of post treatment symptomatic edema. They concluded that a tumor margin dose from 12 to 16 Gy represents the therapeutic window for benign meningioma radiosurgery thus reaching the goal of delivering a therapeutic radiation dose without increasing toxicity rates (Kollova et al., 2007, Liscak et al., 2004)(Santacroce et al., 2014).

Conversely in a recent review of the literature no correlation between treatment dose and toxicity after radiosurgery is reported rather a relationship between increasing tumor size and toxicity is onserved ($p < 0.05$) (Bloch et al., 2012).

According to other reports tumor location is also a risk factor, reporting higher toxicity for large tumours located in the convexity/parasagittal region more frequently developing symptomatic edema after radiosurgery(Kollova et al., 2007, Kondziolka et al., 1998, Sheehan et al., 2015a)(Santacroce et al., 2014).

4.3 Radiosurgery and Stereotactic Fractionated Radiotherapy

Fractionated stereotactic radiotherapy, conversely to radiosurgery, combines the step dose gradients of high conformal radiation with the radiobiological effect of dose fractionation (Santacroce et al.,2014).There is a big debate among physicians whether the one or the other radiation technique be safer and more effective with respect to clinical and imaging outcome respectively(Santacroce et al., 2014). It is not aim of this doctoral work to compare those radiation techniques. In order to clarify these points there are several contributions which explain how from one side the biological efficacy of both stereotactic radiation techniques (Elia et al., 2007)(Santacroce et al., 2014).

The rationale to dose fractionation is to spare the nervous tissue adjacent to the target from late complications given the low α/β ratio of 2 assumed using the linear quadratic formula for biological and thus described as late responding tissue. Assuming the same α/β ratio value of 2 for benign meningiomas, there is no radiobiological advantage of dose fractionation with respect to imaging tumour control (van der Kogel, 1991).

We have already detailed about the differences between SFRT and RS (Santacroce et al., 2014). These can be summarized as follows:

- Imaging response rate: imaging response rates are comparable. Nevertheless given the common definition of imaging tumour control as stable or shrinking size of the target volume (Santacroce et al., 2012, Elia et al., 2007) RS results in a higher imaging shrinkage rate compared to fractionated stereotactic radiotherapy. On the contrary there is no difference with respect to clinical response and neurological improvement rate.
- Toxicity rate: higher incidence of toxicity after RS by increasing target volume and tumour location in eloquent areas like anterior visual pathways, brainstem or convexity compared to SFRT. (Kollova et al., 2007, Pollock et al., 2012a, Pollock et al., 2012b, Barami et al., 2007, Elia et al., 2007, Bloch et al., 2012)
- Treatment time: a dose fractionated schedules requires 6 weeks of treatment given a dose schedule of 1,8 Gy daily dose to a cumulative dose of 54Gy.
- Radiation fields: SFRT is usually indicated for those target whose shape , volume and intracranial location does not allow a single session radiation, given the risks that RS might imply. In this case bigger radiation fields are mandatory and dose fractionation schedules are required

Apart from these major differences the radiation applied, the energy and the biological efficacy of both techniques are identical. It must be said that dose fractionation schedule for benign WHO Gr I meningiomas as for imaging defined meningioma range from 50,4 Gy to 54 Gy with a daily dose of 1.8 Gy is biologically identical to those applied in single session setting (Pollock et al., 2012a, Pollock et al., 2012b). Interestingly new contributions report about the equivalent biological efficacy of highly conformal hypofractionated stereotactic radiotherapy as comparable to both SFRT and RS, thus confirming that the estimations of biological effective doses for each radiation technique are comparable (Han et al., 2014, Morimoto et al., 2011).

A very honest and objective review about stereotactic radiation techniques (Elia et al., 2007) has clearly explained that neither RS nor SFRT show an absolute superiority on another, but should be used as complementary treatment indication to fractionated stereotactic radiation over radiosurgery is for large target volumes close to critical structures and optic nerve sheath meningiomas with preserved vision (Kondziolka et al., 2008). This gives a rationale to stereotactic dose fractionation when therapeutic dose in single session cannot be applied.

4.4 Radiosurgery and microsurgery

As already mentioned radical microsurgical resection is still the treatment of choice for intracranial meningiomas. (Santacroce et al., 2012)

However the morbidity rate associated with the aggressive resection of many meningiomas located along the skull-base or involving the dural sinuses can be significantly high (Santacroce et al., 2014). Therefore many authors suggest a planned sub-total tumor removal or so called “debulking”, now often performed to reduce the volume of tumor mass to make a post-operative RS easier to achieve by reducing chance of new postoperative neurologic deficits (Pollock et al., 2012, Santacroce et al., 2014).

As already reported (Santacroce et al., 2014) a comparison of big radiosurgery series with a microsurgery series in a specific intracranial location is hard to be achieved in a reliable way, due to variability in terms of shape, volume of meningiomas and critical neurovascular structures adjacent to them; besides a big bias of such a comparison is the primary indication to a radiati0on therapy given when microsurgery being not possible and said this underestimating the risks of microsurgery and overestimating the rate of success of RS.

A recent review of the literature about outcomes and quality of life after meningioma microsurgery (Huang et al., 2011) report a detailed surgical outcome according to meningioma location. Morbidity rates ranged from 8 to 10 % for convexity/parasagittal and falcine meningiomas and from 0 to 61.5 % for skull base meningiomas respectively. Mortality

rates for convexity/parasagittal and falcine meningiomas were reported to range from 0 to 3 % conversely for skull base tumours from 0 to 8.7 %. Functional improvement was reported at 55 % for patients harbouring a convexity meningioma and ranged from 0 to 100 % for patients operated for skull base meningioma (Santacroce et al., 2014)

These outcomes are then compared with stereotactic radiotherapy and radiosurgery series reporting outcomes of imaging tumour control ranging from 90 to 100 % and clinical improvement from 13 to 53 %. These results confirm the largest contributions reported so far (Pollock et al. 2012 ; Kondziolka et al. 2008; Kollova et al. 2007 ; Santacroce et al. 2012). The authors conclude that since resection for skull base meningiomas is often limited owing to involvement of critical neurovascular structures radiosurgery is an appealing option and to be considered as treatment option for small to medium sized skull base meningiomas(Santacroce et al., 2014).

Although radiation therapy does not achieve tumour removal in case of benign meningiomas some new evidences **show** how heroic efforts to remove all affected dura and bone should be discouraged to minimize the risk of postoperative neurologic deficits. Recently Sughhrue reviewed the tumor recurrence rate of 373 patients with WHO grade I meningiomas having surgery from 1991 to 2008. With a median follow- up of 3.7 years, there was no difference in the 5-year recurrence rates for patients having Simpson grade I–IV resections. (Sughrue et al., 2010)

These outcomes were then commented by Sheehan (Santacroce et al. 2012) suggesting that the benefits of Simpson grade I vs. grade II resections may be negligible, coupled with the validated efficacy of radiosurgery for meningiomas, is resulting in a paradigm shift in neurosurgery.

Although the sample has median follow up timeframe which is not long enough for a benign meningioma, suggests an approach of intentional cytoreductive surgery leaving behind small

portions of tumor adjacent to critical neurovascular structures, bone, or dura, followed by radiosurgery to treat the residual meningioma. First short term results are relatively promising. Furthermore patients undergoing primary radiosurgery have not been exposed to the risks of open surgical procedure brain exposure brain retraction anaesthesia, intensive care stay. Recently Kondziolka commented: How much is that of value? (Kondziolka et al., 2008b).

4.5 Radiosurgery and active surveillance

Historically before radiation therapy was introduced in clinical routine the so called "wait and see" strategy better defined as "active surveillance" was the preferred choice the management of remnants, rest or primarily diagnosed and not operable benign meningiomas

We have already stressed the point about the rarity of a pure incidental finding of meningioma (Santacroce et al., 2012) according to the study from Vernooij and co-workers. (Vernooij et al., 2007).

Interestingly this observation is finding a large number of confirmations in more recent reports, not only with respect of RS often supported by neurosurgeons who envisioned it but also by many colleagues radiation oncologists after delivery of dose fractionated technique like SFRT, external beam radiation Therapy (EBRT) and intensity modulated Radiotherapy (IMRT). Rogers and colleagues (Rogers et al., 2015, Rogers and Mehta, 2007) have stated that after subtotal resection, radiation therapy improves local control, and in some series, survival. It is well known that the lack randomized data to support this observation is a big limitation; it is still debatable whether these patients should be carefully observed or treated pre-emptively. The authors conclude that this decision is complex to make, given that some patients will do well for many years after subtotal resection alone. Nevertheless the role of highly conformal radiation therapy, independently from the technique used, seems to be

gaining an emerging role in clinical management of meningioma thus confirming the “shift” in treatment protocols addressed by Sheehan (Santacroce et al., 2012)

4.6 Radiosurgery and operator’s experience

The present doctoral thesis is focused on imaging tumour control rates of radiosurgery for benign meningiomas. A very intriguing finding is the influence of the “centre effect” on imaging outcome. According to our analysis in both univariate and multivariate setting the variable “centre” was predictive factor on PFS rate. Worse imaging outcome is observed in the pioneering era and in less experienced groups in more recent times (Santacroce et al., 2012).

One of the most intriguing aspects of such a result is the enormous variability observed by the principal investigator (PI): the radiation fields applied, the dose concepts, the number of shots used and the number of conic collimators tend to vary greatly form centre to centre given a common target volume. This might explain the significant difference of outcomes among centres und how has a statistical predictive role ($p<0.0001$)(Santacroce et al., 2012).

A key point is to define common guidelines and consensus about target volume contouring and arrangement of radiation fields and dose concepts which are currently lacking. The doctoral thesis is based only on Gamma Knife based RS.

To make this issue even more complex is the paucity of data about the technical difference between different devices capable to deliver stereotactic photon radiation (LINAC, GK, CK) which should be taken into account when performing RS or SFRT.

As for microsurgery, radiosurgery is to a considerable extent operator dependent, and the individual experience of the operator may have the same importance as in microsurgery (Santacroce, Kamp et al., 2014)

5 Conclusions

This doctoral work aims to detail about the role of stereotactic single session radiation therapy for benign intracranial meningiomas. As already detailed the delivery of a high dose of ionizing radiation can be performed with different techniques based on photon emission (Santacroce et al., 2014). Although the data report only about radiosurgery GK based there are nowadays also other radiation devices such as CK or dedicated linear accelerators which are able to perform highly conformal stereotactic radiotherapy either in single session as well as dose fractionated. The technology the physics and the characteristics of each device are to be cautiously considered when delivering stereotactic radiation in order to achieve an optimal dose distribution.

Patient with a benign meningioma have many powerful options to reach a cure defined as tumour remission and imaging/clinical control(Santacroce et al., 2014).

Benign intracranial meningioma can undergo both microsurgery and radiosurgery. Radiosurgery provides a high chance of reaching an imaging/ clinical tumour control, given the compromise that should be considered between the risks of open surgical resection and the simple tumour control without reaching a remission of the meningioma irradiated (Santacroce et al., 2014).

In order to spare the cerebral tissue from radiation exposure small target volume, a sharply defined target, accurate dose delivery avoiding under dosing and high conformity are key points for optimal treatment(Santacroce et al., 2014, Flickinger et al., 2008). Gross total resection is the preferred treatment of benign meningiomas, in particular for tumours needing decompression of neuro-vascular structures (Santacroce et al., 2014).

Radiosurgery is a safe and effective method of managing benign intracranial meningiomas either recurring after resection or incompletely resected (Santacroce et al., 2012, Pollock et al., 2012b, Kondziolka et al., 2008b)(Santacroce et al., 2014).

The data show further convincing evidence of radiosurgery also as primary treatment for those tumours not achievable to resection due to unacceptable risk of perioperative morbidity(Santacroce et al., 2013, Santacroce et al., 2012).

Analysis of the imaging tumour control rates shows better outcomes for skull base location, female gender, sporadic and imaging-defined (not previously operated) tumours(Santacroce et al., 2012)(Santacroce et al., 2014). The low neurological morbidity rate indicates patient safety. Clinical improvement is reported in 50 % of patient treated and complete resolution of symptoms in 20 % of patients treated (Santacroce et al., 2012)(Santacroce et al, 2014). Indication for radiosurgical treatment should be given for: tumour remnant or recurrence after surgical resection, with maximum major tumour diameter, 3 cm and with acceptable dose delivery to adjacent eloquent structures; symptomatic primary tumours in locations associated with higher risk for resection with maximum major tumour diameter, 3 cm and with acceptable dose delivery to adjacent eloquent structures; concomitant medical illnesses or advanced age, in younger patients who chose radiosurgery over other available options; patients with minimal symptoms or asymptomatic who chose against observation(Santacroce et al., 2014). Contraindications include large tumour volume (mean diameter >3 cm or target volume > 12cc), tumours with symptomatic optic nerve or chiasma compression, optic nerve sheath tumours with preserved vision, elderly patients with asymptomatic tumours, or tumours with atypical imaging features and no prior histological diagnosis (Kondziolka et al., 2008b)(Santacroce et al., 2014).

Clinical observation with serial imaging should be reserved for asymptomatic elderly patients with calcified convexity/parasagittal meningiomas (Santacroce et al., 2012, Kollova et al., 2007). Fractionated stereotactic radiotherapy is recommended over radiosurgery for larger tumours or close to critical structures (less than 2–4 mm) (Elia et al., 2007) and all cases of optic nerve sheath meningiomas with preserved vision (Kondziolka et al., 2008b). To

conclude the operator´s experience plays a very crucial role when performing radiosurgery(Santacroce et al., 2012).

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Eidesstattliche Versicherung

Ich versichere an Eides statt, dass die Dissertation selbständig und ohne unzulässige fremde Hilfe erstellt und die hier vorgelegte Dissertation nicht von einer anderen Medizinischen Fakultät abgelehnt worden ist.

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